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Harnessing the Power of Furfuryl Cations: The Aza-Piancatelli Rearrangement and Beyond

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

by

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Veits, G. K.; Read de Alaniz, J. *Dysprosium trifluoromethanesulfonate, Encyclopedia of Reagents for Organic Synthesis* **2014**, 10.1002/047084289X.rn01662.

Veits, G. K.; Read de Alaniz, J. *Dysprosium (III) Catalysis in Organic Synthesis*, *Tetrahedron* **2012**, *68*, 2015 – 2026.

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ABSTRACT

Harnessing the Power of Furfuryl Cations:

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The ubiquity of amine functional groups in all of nature as well as a large majority of pharmaceutically active molecules makes methodologies capable of quickly constructing carbon–nitrogen bonds invaluable. Reactions capable of constructing these highly desirable bonds in addition to introducing molecular complexity are highly sought-after. Therefore we set out to develop a novel cascade rearrangement of furylcarbinols, a sustainable starting material, to 4-aminocyclopentenones, the aza-Piancatelli rearrangement.

Inspired by Piancatelli's rearrangement of furylcarbinols with water to form 4-hydroxycyclopentenones for the synthesis of prostaglandins, we explored the rearrangement with amine nucleophiles to access valuable 4-aminocyclopentenones. The product-forming cascade is initiated by dysprosium trifluoromethanesulfonate, a relatively underdeveloped Lewis acid catalyst. Activation results in the formation of a furfuryl cation (oxocarbenium ion) that is intercepted by an amine nucleophile and terminates in a 4π conrotatory electrocyclization establishing the observed *trans*-stereochemistry. The chemistry was initially developed with aniline nucleophiles, and was later extended to substituted hydroxylamines. Mechanistic investigations of the aza-Piancatelli rearrangement have shown that an off-cycle binding of the dysprosium catalyst and the amine nucleophile controls the rate, as observed by a Hammett plot. However, the selectivity of the

rearrangement is determined by the ability of a nucleophile to efficiently capture the oxocarbenium ion upon its formation.

The value of the aza-Piancatelli rearrangement has been highlighted by the synthesis of an hNK1 inhibitor and by efforts toward the total synthesis of homoharringtonine, a pharmaceutical drug approved for the treatment of chronic myeloid leukemia. Additionally, a Piancatelli rearrangement of macrocyclic furylcarbinols, to be applied to the total synthesis of coralloidolide F, has been explored.

Finally, chiral phosphoric acids such as (R)-TRIP have been found to be catalysts for the aza-Piancatelli rearrangement capable of inducing enantioselectivity. This is the first example of asymmetric cascade rearrangements of its kind.

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LIST OF ABBREVIATIONS

Å	Angstrom
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
CAN	ceric ammonium nitrate
ccw	counter-clockwise
CML	chronic myeloid leukemia
CSA	camphorsulfonic acid
cw	clockwise
D_0	dissociation energy of the Ln–O bond
DASA	donor-acceptor Stenhouse adduct
DCE	1,2-dichloroethane
DFT	Density Functional Theory
DHF	dihydrofuran
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
$Dy(OTf)_3$	Dysprosium trifluoromethanesulfonate
EDG	Electron donating group
ee	enantiomeric excess, as calculated by the formula ee = ((R–S)/(R+S))x100
equiv	equivalent

er	enantiomeric ratio, defined as the ratio of one enantiomer to the other R:S
EWG	Electron withdrawing group
FDA	Food and Drug Administration
FMO	Frontier Molecular Orbital
Fmoc	fluorenylmethyloxycarbonyl
GC	gas chromatography
h	hour
HFIP	hexafluoroisopropanol
HOMO	Highest Occupied Molecular Orbital
HOTf	trifluoromethanesulfonic (triflic) acid
HPLC	high-performance liquid chromatography
IC_{50}	half maximal inhibitory concentration
IPA	isopropyl alcohol, 2-propanol
LUMO	Lowest Unoccupied Molecular Orbital
m	*meta*
$MeNO_2$	Nitromethane
min	minute(s)
MeCN	acetonitrile
MS	mass spectrometry
NaBArF	Sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
NBO	natural bond orbital
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*

PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
PhMe	toluene
PMA	poly-phosphomolybdic acid
PMP	*para*-methoxyphenyl
PPA	polyphosphoric acid
p-TSA	*para*-toluenesulfonic acid
quant	quantitative
r	ionic radius
RCM	ring closing metathesis
rt	room temperature
SAR	structure-activity relationship
$Sc(OTf)_3$	Scandium trifluoromethanesulfonate/ scandium triflate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	Transition state
Z	charge

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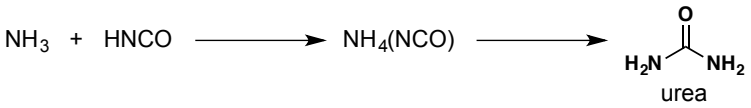
1. Introduction

1.1 The Importance of Organic Chemistry

Friedrich Wöhler's synthesis of urea from cyanic acid and ammonia in 1828 marked the first recorded and recognized synthesis of an organic substance from inorganic starting materials, a discovery considered to be the starting point of organic chemistry and the end of vitalism (Scheme 1.1).[1]



Scheme 1.1. Wöhler synthesis of urea.

Since that discovery, organic chemistry has come a long way resulting in significant and important scientific advances. In 1902, Emil Fischer received the Nobel Prize in Chemistry for his work on the synthesis of sugars and purines. This recognition again marked the intrinsic link between biology and organic chemistry. By this point, organic chemistry had already come a long way from the accidental synthesis of small molecules to a concrete understanding of reactivity and the building of small molecules. The synthesis targets chosen by synthetic chemists are becoming more complex as our understanding of organic chemistry and our synthetic toolbox continues to expand. Modern organic synthesis greatly benefited from the game-changing contributions made by Robert Burns Woodward, who not only advanced the field from a synthetic standpoint, but also from a more fundamental physical organic standpoint. He was awarded the 1965 Nobel Prize in Chemistry "for his outstanding achievements in the art of organic synthesis". His landmark synthetic achievements include the synthesis of cortisone (**1**),[2] cholesterol (**2**)[3] and strychnine (**3**),[4] among others (Figure 1.1). The immensity of his synthetic achievements can be put in

perspective when considering that since Woodward's synthesis of strychnine, there have been seventeen successful approaches to the molecule, the latest one a 2011 synthesis by the Vanderwal group.[5] It is absolutely amazing to think that a synthesis that took 28 steps to complete in 1954 has been shorted to a longest linear sequence of just 6 steps in 2011.

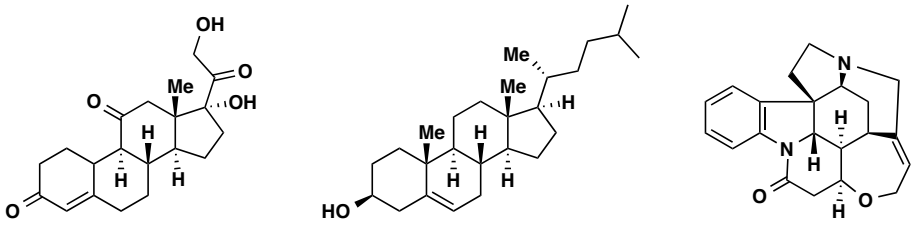


Figure 1.1. Landmark total syntheses accomplished by Woodward.

Following Woodward's and others great contributions to organic chemistry, Elias James Corey's concept of retrosynthetic analysis became perhaps the most valuable contribution to the field of natural product synthesis.[6] Nowadays, total synthesis targets are routinely deconstructed into strategic building blocks using retrosynthetic analysts.

Essential to these natural products and targets of synthetic efforts throughout time are compounds that have interesting biological activity. One commonality among many biologically active compounds is the presence of one or more carbon bound nitrogen atoms. In fact, the precise position of carbon-nitrogen bonds within a molecule are often responsible for the inherent biological activity.[7] Perhaps the fact that the birth of organic chemistry involved the synthesis of a nitrogen-containing molecule – uric acid – was foreshadowing the importance of carbon-nitrogen bond formation in the field. Due to the ubiquity and necessity for strategically placed carbon nitrogen bonds in natural products and pharmaceutically active compounds, there has been great interest in the development of efficient and selective carbon-nitrogen bond-forming methodology. Our group's interest in carbon-nitrogen bond forming methodology while introducing molecular complexity to

readily available starting materials forms the basis of this doctoral thesis. To achieve this in a rational and sustainable manner, we sought to develop a new cascade rearrangement that terminated with an electrocyclic reaction. The core concepts that are incorporated into our rational design are detailed below.

1.1. Electrocyclic Reactions

Electrocyclic reactions fall under the umbrella of pericyclic reactions that also includes cycloaddition reactions, such as the Diels–Alder reaction, sigmatropic rearrangements, such as the Claisen rearrangement, and ene reactions. By definition, a pericyclic reaction involves the making or breaking of bonds through a cyclic array of interacting orbitals. Pericyclic reactions proceed through a concerted mechanism that entails no observable intermediates along the reaction coordinate (Figure 1.2).

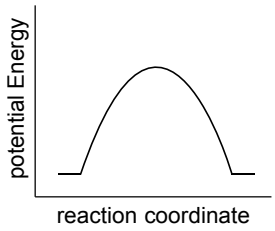


Figure 1.2. Reaction coordinate diagram of a concerted pericyclic reaction.

In their ground-breaking 1964 publication, Robert Burns Woodward and Roald Hoffmann described pericyclic reactions with the concept of conservation of orbital symmetry, a discovery that led to the bestowal of the 1981 Nobel Prize in Chemistry to Hoffmann (Woodward passed away in 1979).[8] The collection of research in this area is widely known as the Woodward-Hoffmann rules. The conservation of orbital symmetry describes the formation of bonds during electrocyclic reactions in terms of the correlation between the Highest Occupied Molecular Orbital (HOMO) of the starting material and the product. This analysis accounts perfectly for the observed conrotation in electrocyclizations

of systems containing 4n π electrons as well as the disrotation observed in 4n+2 π systems (Figure 1.3).

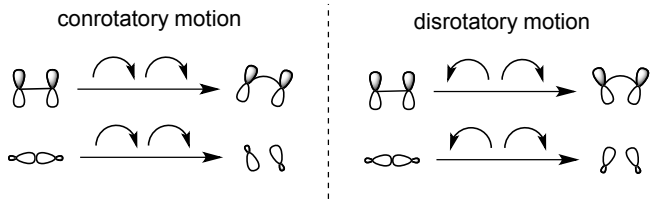


Figure 1.3. Conrotatory and disrotatory motion in electrocyclizations.

Kenichi Fukui, who shared the 1981 Nobel Prize with Hoffmann expanded on the original explanation of orbital symmetry with his Frontier Molecular Orbital (FMO) theory.[9–12]

The concept is best explained pictorially with butadiene and 1,3,5-hexatriene serving as simple examples for the 4π and 6π electron systems, respectively. An analysis of the frontier molecular orbitals shows that in the case of a 4π system, conrotation along the C_2 axis results in overlap of orbital nodes of the same sign, conserving symmetry and resulting in a process that is allowed (Figure 1.4). Disrotation of the 4π system leads to forbidden and unproductive overlap of orbitals of opposite signs.

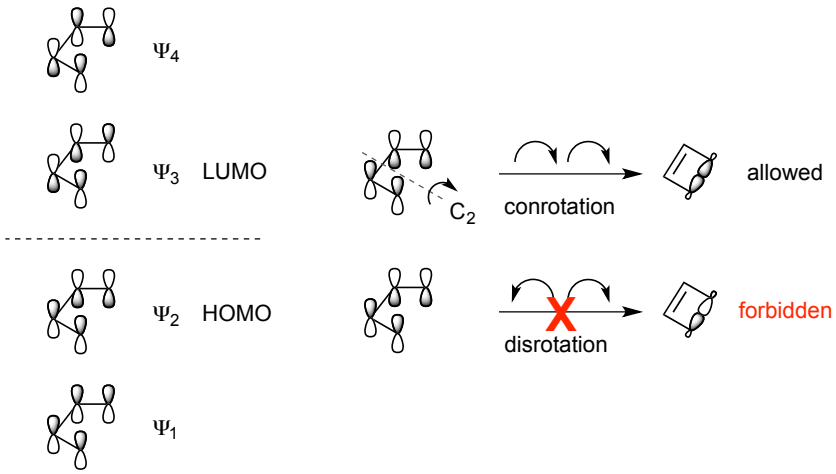


Figure 1.4. 4π Conrotatory electrocyclization.

Analysis of the 6π system shows that conrotation along the C_2 axis results in an interaction of orbitals of opposite signs and is therefore forbidden (Figure 1.5). However, disrotation results in overlap of orbitals of the same sign and is therefore allowed and favored in these systems. It should be noted that as a gross generalization, photochemical processes proceed in the exact opposite manner. Pathways that are thermally forbidden are photochemically allowed, while thermally allowed pathways are photochemically forbidden meaning that in a photochemical setting 4π systems undergo disrotation, while 6π systems will undergo conrotation.

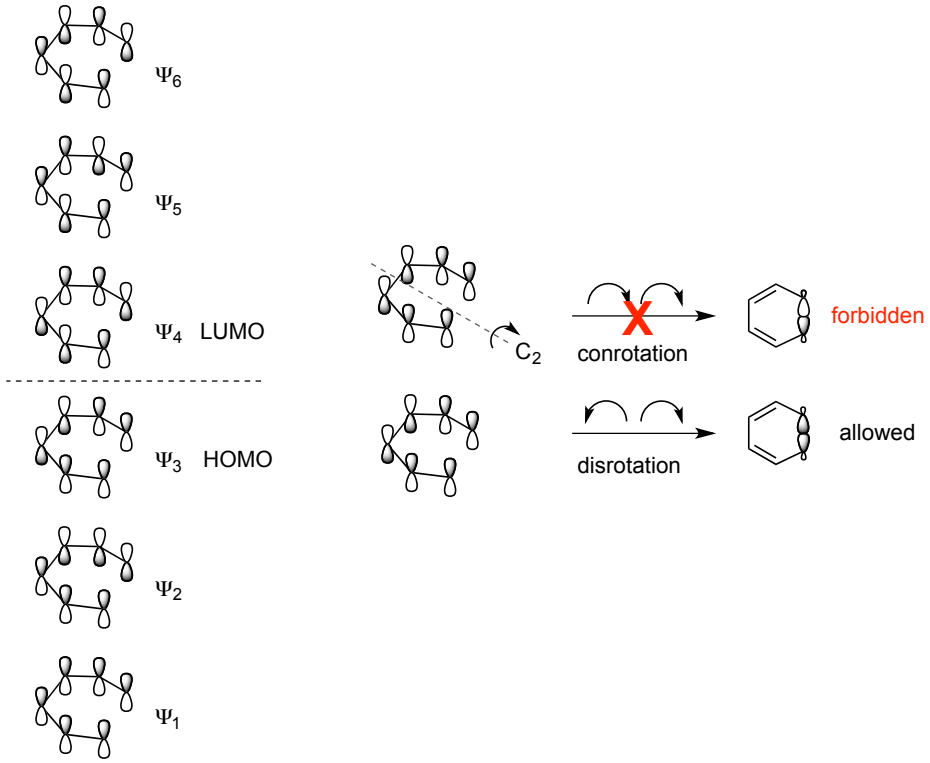


Figure 1.5. 6π Disrotatory electrocyclization.

Since this original description in terms of orbital symmetry and FMOs, a number of other methods have been used to explain electrocyclizations, including aromatic transition state (TS) theory and Möbius/Hückel analysis.[13]

The concerted nature of electrocyclization is the root of one of the magnificent features of this class of reactions: a conservation of stereochemistry. Bond formation in a single step with no intermediates results in an inability for pendant groups to scramble during the bond-forming process. In fact, it was the observation of stereospecificity in these electrocyclizations that led Woodward and Hoffmann to their Nobel Prize winning discovery of conservation of orbital symmetry. In practical terms, this means that the arrangement of R groups around the π bonds of the system will directly translate to the stereochemistry of the observed product, and the same is true for the reverse ring-opening reaction. For example, cyclobutene **4** will ring-open to form diene **5**, while cyclobutene **6** will ring-open to form diene **7**, in agreement with the prescribed conrotatory mode of rotation (Figure 1.6). Triene **8** undergoes disrotatory cyclization to form *cis*-substituted cyclohexadiene **9** (Figure 1.6).

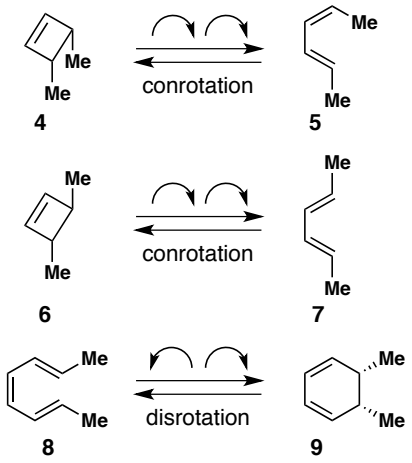
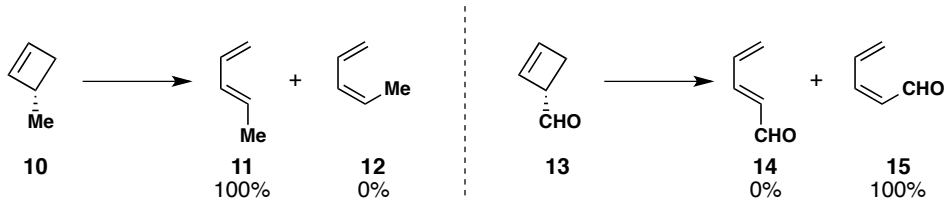


Figure 1.6. Examples of conrotatory and disrotatory motion and their steric outcomes.

In search of a better model and explanation for the observed stereoselectivity, Houk and co-workers examined a series of ring-opening reactions of cyclobutenes with various substituents.[14] Remarkably, methyl-substituted cyclobutene **10** forms **11** exclusively, while

12 was not observed (Scheme 1.2). In the case of aldehyde-substituted cyclobutene **13** however, the observed products was **15** and diene **14** was not formed.



Scheme 1.2. Torquoselectivity in electrocyclizations.

This observed directional conrotation is designated with the term torquoselectivity and is controlled by the electronics of the substitutents.[15,16] Houk found that in general, a donor group will rotate outward, while an acceptor group rotates inward due to stabilization gained from orbital overlap during the ring-opening event (Figure 1.7).

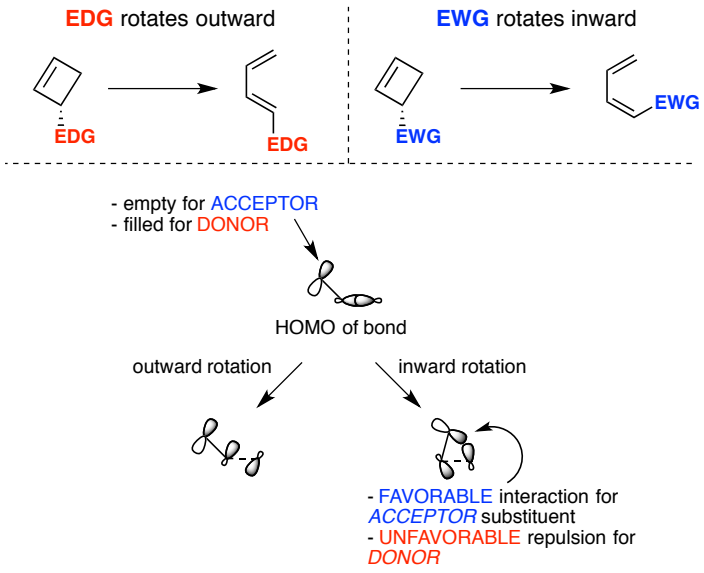
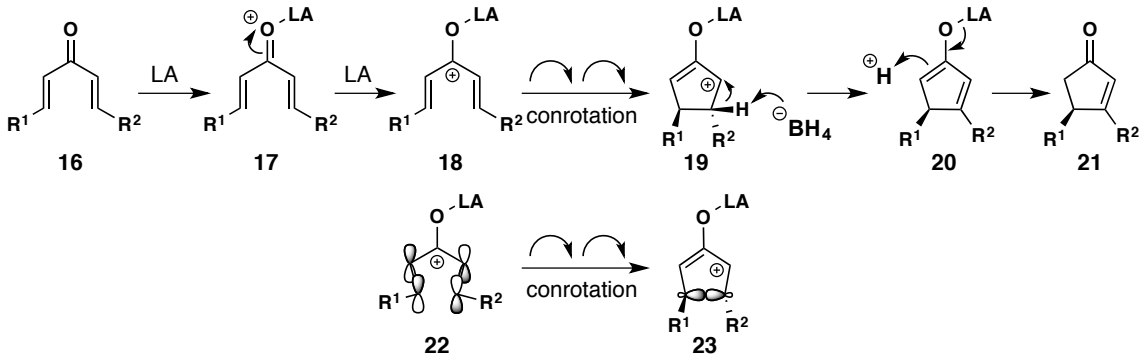


Figure 1.7. Effects of donor and acceptor groups on torquoselectivity.

To me, the beauty of pericyclic reactions lies in their relative simplicity, which is often translated into rather complex products.

1.2. The Nazarov Cyclization

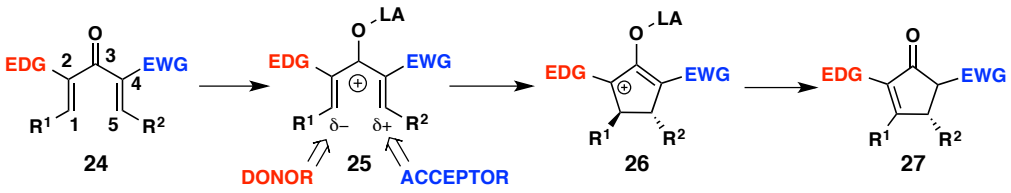
The rules governing the illustrative systems described above also apply to the 4π conrotatory process that governs the Nazarov cyclization. Although it was not correctly identified at the time, the first example of a Nazarov reaction in the literature was described by Vorländer in 1903 when he carried out the reaction of dibenzylidene acetone with concentrated sulfuric acid and acetic anhydride.[17] Almost 40 years passed before Ivan Nazarov published his work on the formation of cyclopentenones 1941 which came to be associated with his name.[18] The Nazarov cyclization generally describes the formation of a cyclopentenone from a divinyl ketone (**16**) under strongly acidic conditions and involves the generation of a pentadienyl cation (**18**) that undergoes a 4π conrotatory electrocyclization to form an oxyallyl cation (**19**) which, upon deprotonation, forms the desired cyclopentenone (**21**) (Scheme 1.3).



Scheme 1.3. Mechanism of the Nazarov cyclization.

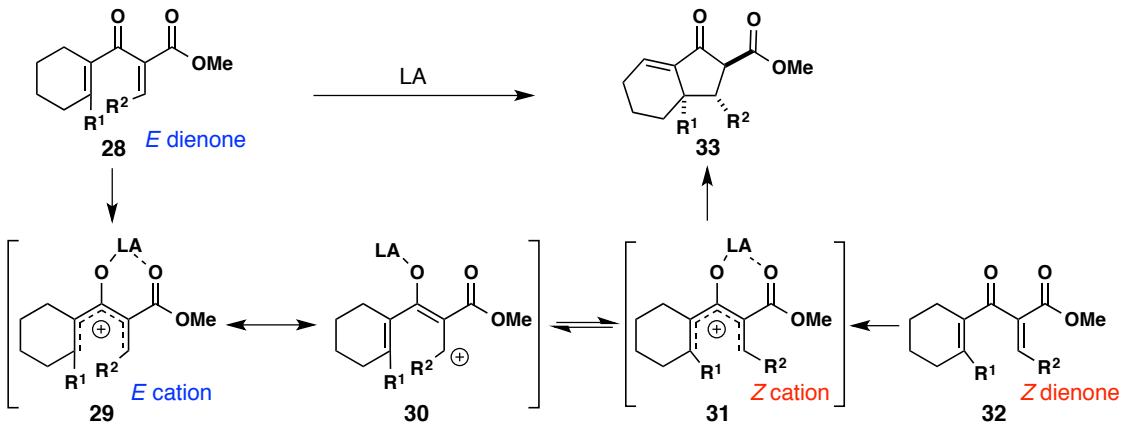
Much progress has been made in the area of the Nazarov cyclization, and these developments have been beautifully summarized in reviews by Denmark,[19] Tius,[20] Frontier,[21] West,[22] and Read de Alaniz.[23] Within these reviews, publications addressing some of the problems associated with the classic Nazarov cyclization, such as the lack of stereoselectivity in the proton elimination step, and the need for stoichiometric acid are

detailed. Frontier's study of the effect of substituents along the backbone of the divinyl ketone has greatly impacted the understanding of the transformation and requirements for successful control of stereochemistry.[24] Positioning an electron donating group (EDG) at C2 while an electron withdrawing group (EWG) is positioned at C4 of the divinyl ketone (**24**) creates a donor-acceptor system with complementary partial negative and partial positive charges at the C1 and C5 termini of the system, respectively (Scheme 1.4, **25**). This polarization greatly decreases the activation barrier for carbon–carbon bond formation.



Scheme 1.4. Donor/acceptor Nazarov substrates.

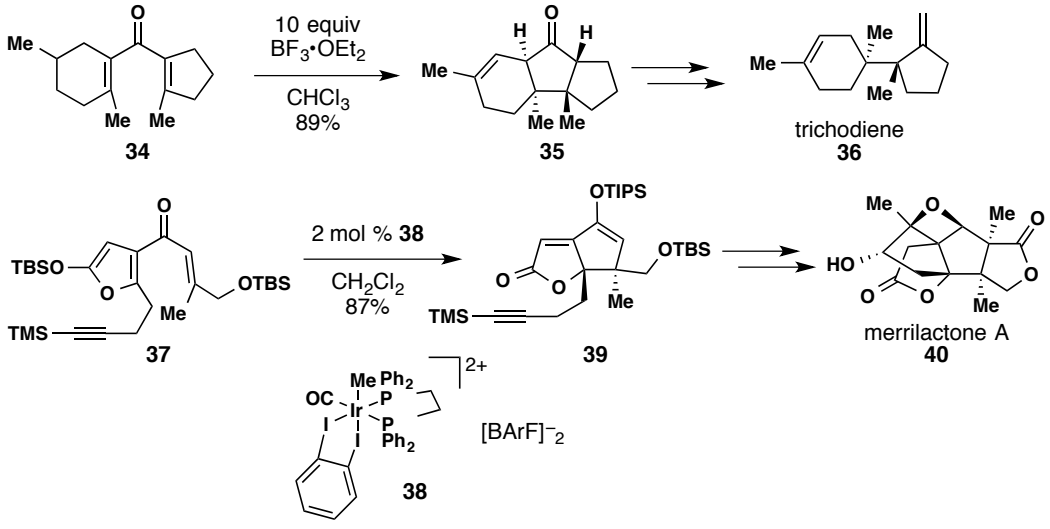
In addition to the formation of a partial positive charge at C5, the EWG at C4 also greatly influences the geometry of the substrate-catalyst binding as well as the catalyst turnover. Shown in Scheme 1.5 is the effect of the EWG on the *E*/*Z* isomerization of the C5 substituent (**29** to **31**), which may be necessary for electrocyclization to occur. Additionally, the presence of the EWG may facilitate the reaction by adding a second binding point for the catalyst. With this knowledge in hand, specialized Nazarov substrates can be prepared for optimal results.



Scheme 1.5. *E*/*Z* Isomerization preceding electrocyclization in donor/acceptor Nazarov substrates.

Since cyclopentenones are ubiquitous in nature, the Nazarov cyclization has been successfully applied to a number of natural product syntheses, including the synthesis of trichodiene (**36**) by Harding and Frontier's synthesis of merrilactone A (**40**) (Scheme 1.6).[25,26]

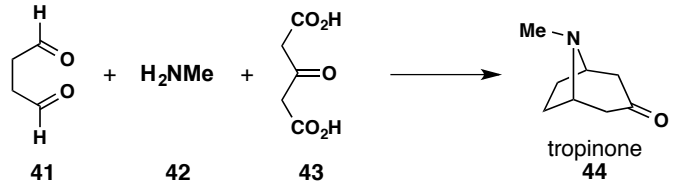
One great feature of the Nazarov cyclization is the relative ease with which quaternary carbon centers can be formed via the electrocyclic bond-formation. Wenz and Read de Alaniz summarized the successes with this approach in a recent review.[23]



Scheme 1.6. Total synthesis of trichodiene and merrilactone A via Nazarov cyclizations.

1.3. Cascade Processes

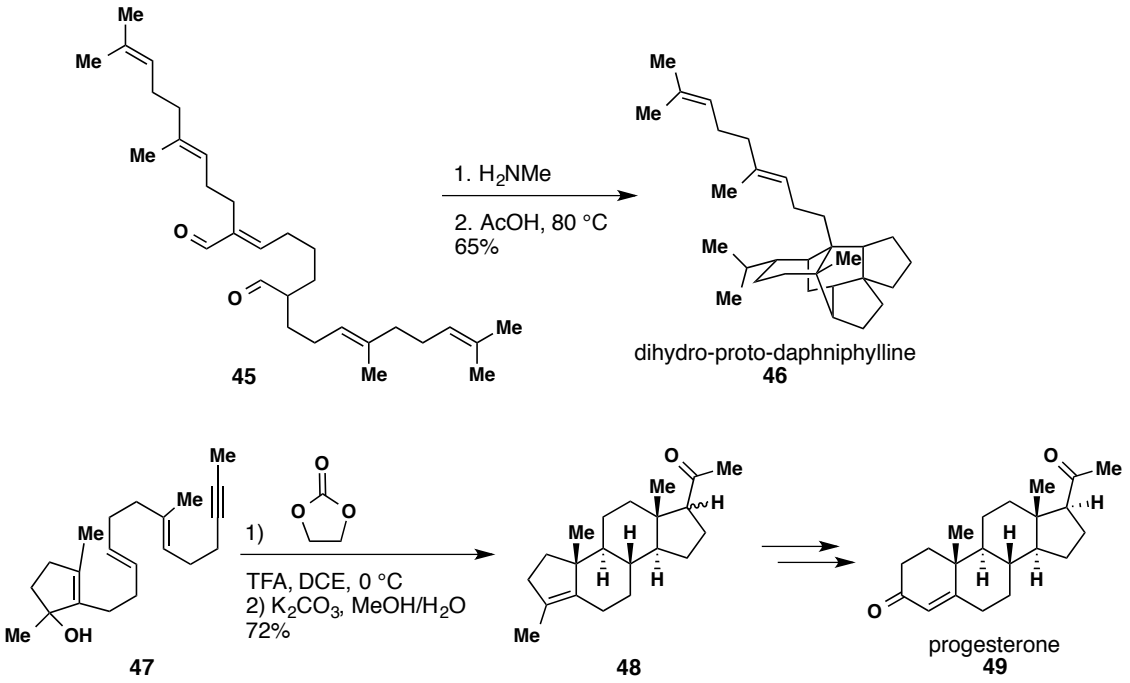
The process of forming and breaking bonds to carbon forms the basis of organic chemistry, where the goal is to do so in a well defined, controlled manner. Most often, a synthetic method is developed that allows for the formation of one new bond throughout the course of a reaction. However, in terms of ideal processes, it is much more desirable to develop reactions where multiple bonds form during a single reaction. Such transformations are classified as domino or cascade reactions. By definition, domino reactions are transformations during which two or more bonds (usually carbon–carbon) are formed.[27] In analogy to dominos falling, a single activation step – pushing the first domino stone - is required that results in a cascade of bond-forming steps – domino stones falling – that are progressively lower in energy, until a resting state is reached – all of the dominos lie flat on the ground. The first domino reaction resulting in the formation of a natural product was Nobel Prize winner Robert Robinson's one-pot synthesis of tropinone (**44**) in 1917.[28] The synthesis was accomplished via a double Mannich reaction between succindialdehyde (**41**) and methylamine (**42**) in the presence of acetone dicarboxylic acid (**43**) (Scheme 1.7).



Scheme 1.7. Robinson's landmark cascade synthesis of tropinone.

In the synthetic community, the development of cascade processes is highly desirable due to the speed and ease at which complexity can be built. However, despite these positive attributes, cascade processes can be difficult to see or predict, and are often serendipitously discovered during the synthesis of natural products. In some cases of excellent retrosynthetic analysis (possibly combined with a smidge of luck) however, cascade sequences yielding

complex products are not only predicted, but also executed. Illustrative examples include Heathcock's pentacyclization to form dihydro-proto-daphniphylline (**46**) and Johnson's synthesis of progesterone (**49**) (Scheme 1.8).[29,30]



Scheme 1.8. Cascade processes in the synthesis of dihydro-proto-daphnyphylline and progesterone.

In addition to the aesthetically pleasing nature of cascade processes, these transformations also have great practical value in terms of their environmental impact. Performing multiple bond-forming events in a single pot and a single step increases atom economy of the reaction,[31] decreases solvent waste and reactor time associated with the reaction, work-up and purification steps, greatly decreasing the environmental impact of such transformations.

1.4. Sustainable Reaction Design

A relatively recent concept to be applied to organic chemistry is the idea of sustainable reaction design and green chemistry. Considering the birth of organic chemistry involved the use of highly toxic cyanide compounds, the invention of the fume hood is quite a comfort to

modern organic chemists. However, simply ensuring the safety of the chemist while synthesizing valuable chemicals is no longer the sole goal for academics or industry. With increasing awareness of the effects of industrialization and the cumulating carbon footprint on planet Earth, there has been a great shift toward developing new environmentally friendly chemical processes. Paul Anastas' twelve principles of green chemistry are the bible of the green chemist and provide guidelines and rules to orient chemists toward developing reactions and processes that have less of a negative effect on nature.[32] To this end, one of the merits cited for the choice of the 2005 Nobel Prize in chemistry awardees Yves Chauvin, Robert H. Grubbs, and Richard R. Schrock was the fact that for the metathesis methods in organic synthesis allow for short, efficient routes to desired products and contribute to green chemistry. In terms of sustainable reaction design, much work is being done in the area of using sustainable and renewable starting materials. With the undeniable environmental effects and depletion of petroleum sources, there is a great need for the development of reactions using renewable starting materials, such as biomass. To avoid interference with food supply, the ideal material would be a non-edible by-product of the food industry.

1.5. Furfural

The methodology described in this thesis revolves around reactions of furfural derivatives. Furfural is produced from hemicellulose present in agricultural waste, such as corncobs, oat hulls, almond husks, and bagasse. In fact, the Quaker Oats company developed the first industrial scale production of furfural in the 1920s to make use of their cereal waste.[33] Today, annual production of furfural is approximately 300,000 tons per year, and can be purchased from Aldrich at a price of $95 for 3 kg. Since it is produced from a non-edible byproduct of the food industry and is very cheap, furfural is an excellent choice of sustainable starting material for applications in synthesis and materials chemistry.

In terms of its chemistry, furfural is very versatile. Compared to the 36 kcal/mol resonance energy of benzene, the aromatic stabilization of the furan ring is relatively low at only 16 kcal/mol, even compared to its closer cousins thiophene (29 kcal/mol) and pyrrole (22 kcal/mol). This allows for reactions under relatively mild conditions. The furan unit can serve as the source of a 1,4-dicarbonyl,[34] an olefin, a diene[35] or an enol ether.[36,37]

The reactivity of furan has been exploited in synthetic methods developed by Achmatowicz,[38] Piancatelli[39] and Batey[40], all of which rely on rearrangements of furfural or its derivatives to access synthetically valuable scaffolds (Figure 1.8). Additionally, a number of total syntheses of natural products including Henschke's synthesis of prostaglandin analogues,[41] Zakarian's synthesis of (+)-brevisamide,[42] and Wu's synthesis of tonghaosu analogues originate from furfural and its derivatives (Figure 1.8).[43]

In terms of other applications, furfural has been used to synthesize surfactants, ionic liquids, chiral ligands, as well as self-healing polymers.[44–48] There are also ongoing investigations of its use as a biofuel,[49] which would be more desirable than alternative fuels, such as starch based methods, which interfere with food production.

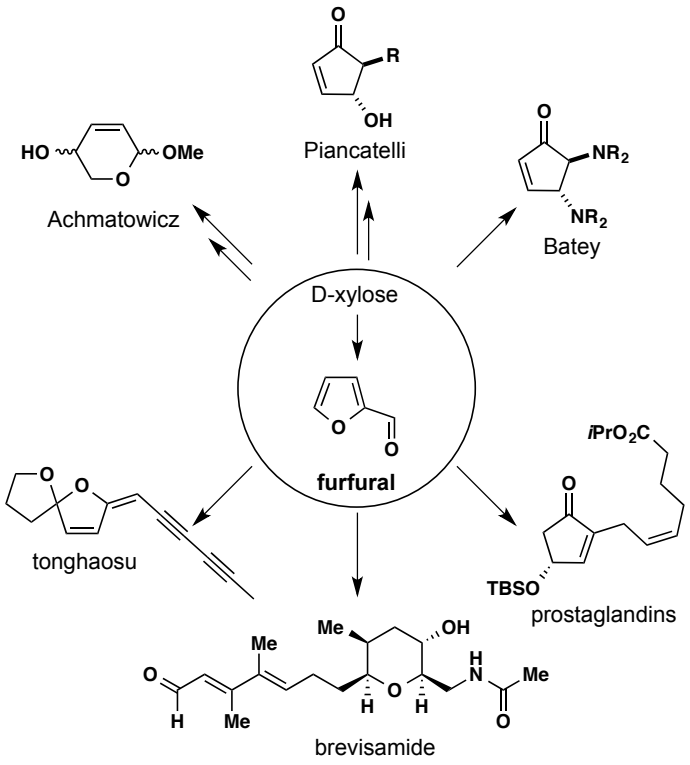
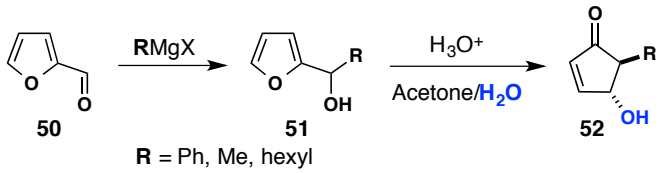


Figure 1.8. Select applications of furfural and its derivatives.

1.6. The Piancatelli Rearrangement

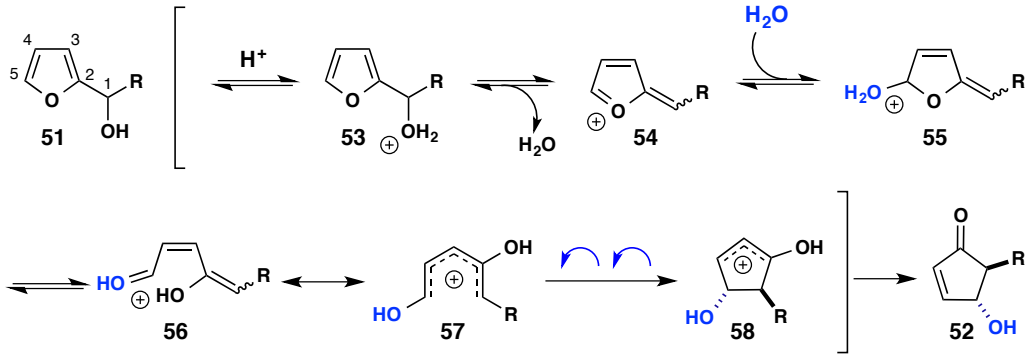
With the determination of the structure and of the importance of prostaglandins by Sune K. Bergström in the 1950s, a discovery that earned him and his student Bengt I. Samuelsson the 1982 Nobel Prize in Physiology or Medicine together with John R. Vane, there came an enormous interest in synthetic methods to quickly access the prostaglandin scaffold.[50] Many of the methods required multiple steps to access the requisite cyclopentenone unit, often by way of a 1,4-diketone. Motivated by the lack of direct routes, Piancatelli developed the synthesis of 4-hydroxycyclopentenones (**52**) directly from furylcarbinols (**51**) (Scheme 1.9).[39] Simple furylcarbinols (**51**) can be accessed in one step via a Grignard reaction between furfural and an aryl or alkyl halide. Exposure of these furylcarbinols to protic acid, such as formic acid, polyphosphoric acid (PPA) or *para*-toluenesulfonic acid (*p*-TSA), in

aqueous solvent initiates a cascade resulting in 5-substituted-4-hydroxycyclopentenones (**52**) in one step, the transformation now known as the Piancatelli rearrangement (Scheme 1.9).



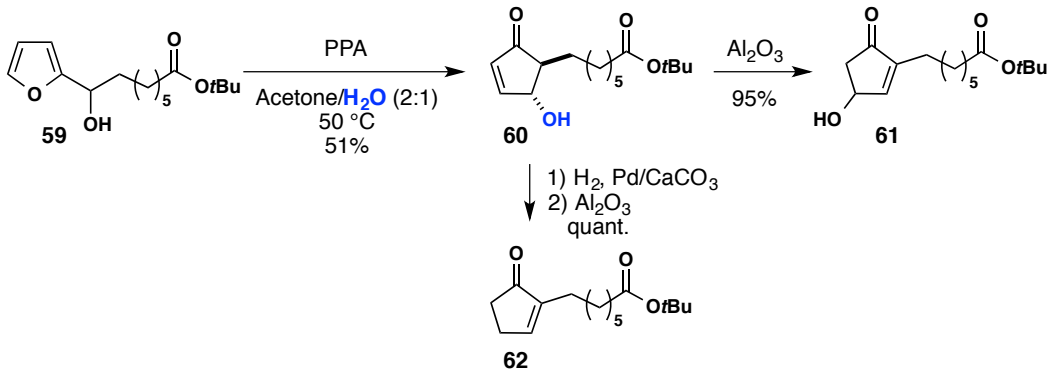
Scheme 1.9. The Piancatelli rearrangement of furylcarbinols.

The reaction proceeds in a stereospecific manner, exclusively furnishing the *trans*-substituted product, which led Piancatelli to invoke a 4π conrotatory electrocyclization as the carbon–carbon bond forming and stereodetermining event. The mechanism is proposed to commence with activation of the alcohol followed by loss of water, generating the highly reactive oxocarbenium ion **54** (Scheme 1.10). Nucleophilic attack at the 5-position of the oxocarbenium ion initiates the productive cascade process that ultimately yields the desired cyclopentenones (**52**). Nucleophilic trapping of the oxocarbenium results in acetal **55**, which can open up to form **56**. Redrawn as a pentadienyl cation, **57** undergoes a 4π conrotatory electrocyclization forming the oxyallyl cation (**58**) that, upon loss of a proton, yields the observed *trans*-substituted 4-hydroxycyclopentenone (**52**).



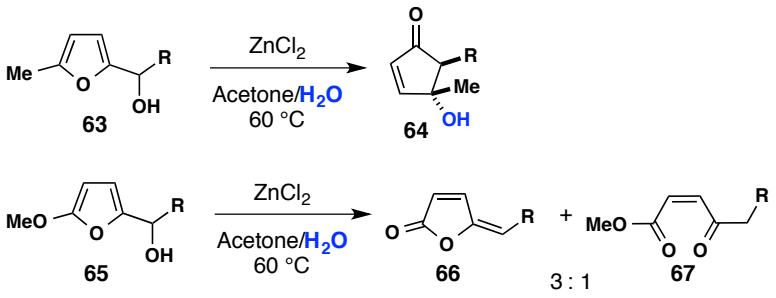
Scheme 1.10. Proposed mechanism of the Piancatelli rearrangement.

In a subsequent publication, Piancatelli demonstrated that a functional group (a *t*-butyl ester) incorporated into the side chain of the furylcarbinol did not interfere with the reaction conditions for the Piancatelli rearrangement (**59** to **60**, Scheme 1.11).[51] Treatment with aluminum oxide facilitates rearrangement to the more stable cyclopentenone (**61**). Alternatively, reduction followed by elimination using aluminum oxide gives cyclopentenone **62**.



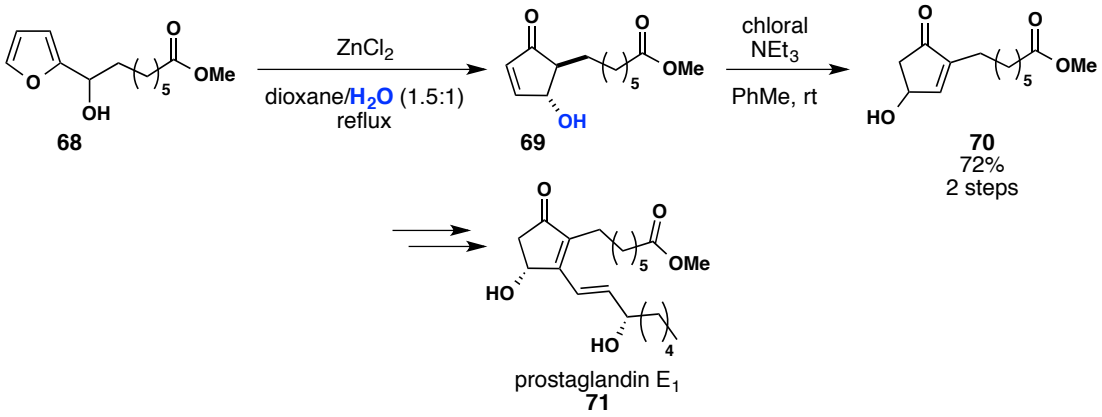
Scheme 1.11. Progress toward prostaglandin synthesis via the Piancatelli rearrangement.

To further expand the utility and general understanding of the reaction, Piancatelli investigated substituents at the 5-position of the furan ring (**63**, Scheme 1.12). The presence of a methyl group required a switch to Lewis acidic reaction conditions due to the decreased stability of the starting materials because of the donating group – conditions which have passed the test of time. One equivalent of zinc chloride efficiently promoted the rearrangement to cyclopentenone **64** (Scheme 1.12).[52] Interestingly, the reaction was stereospecific, resulting in exclusive formation of the product where the alcohol and R-group are *trans* to one another, again pointing to a 4π electrocyclic process. When attempting the transformation with a 5-OMe group, Piancatelli and co-workers found that the Piancatelli rearrangement did not take place, and instead resulted in formation of the 4-ylidenebutenolides **66** and 4-oxo-2-enoic acid methyl esters **67** (Scheme 1.12).[53]



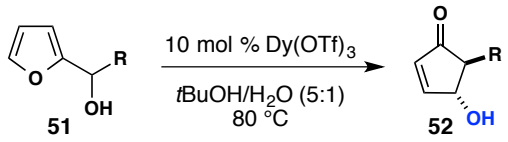
Scheme 1.12. The Piancatelli rearrangement with 5-substituted furylcarbinols.

Since its initial development, Piancatelli's rearrangement conditions have been applied to a number of syntheses of prostaglandins, such as the synthesis of prostaglandin E1 (**71**) by Spur and co-workers (Scheme 1.13).[54] Additional applications and developments can be found in reviews by Piancatelli[37] and by Roche and Aitken.[34,55]



Scheme 1.13. Total synthesis of prostaglandin E_1 via a Piancatelli rearrangement.

More recently, Reiser and co-workers have developed methods that will likely improve the use of the Piancatelli rearrangement in an industrial setting through the development of a microwave-assisted rearrangement of furfuryl alcohol to 4-hydroxycyclopent-2-en-1-one.[56] The group then showed that a microreactor setup allows for rapid synthesis of large quantities of the desired cyclopentenones, with residence times of only 53 seconds. The Read de Alaniz group also developed a new method for the synthesis of 4-hydroxycyclopentenones (**52**) using dysprosium triflate as the catalyst (Scheme 1.14).[57]



Scheme 1.14. Dysprosium triflate catalyzed Piancatelli rearrangement.

These recent advances will greatly benefit the industrial scale production of 4-hydroxycyclopentenones by decreasing the waste associated with the $ZnCl_2$-catalyzed process, as exemplified by the use of 16 equivalents of $ZnCl_2$ (65 kg $ZnCl_2$ for 16 kg of starting material) in Henschke's multi kilogram synthesis of 4-hydroxycyclopentenone.[41]

The Piancatelli rearrangement is a beautiful transformation that takes a simple molecule derived from a sustainable natural resource – furfural – and converts it into a sterically and chemically complex molecule with great synthetic potential. Piancatelli's proposed mechanism, shown in Scheme 1.10, proceeds via a conrotatory electrocyclic ring closure. There is much evidence that the Nazarov cyclization proceeds via this pathway, but an analysis of the Piancatelli rearrangement as a transformation in its own right was necessary. De Lera and co-workers completed a computational study of the Piancatelli rearrangement to determine the viability of a conrotatory electrocyclization pathway.[58] They evaluated possible transition structures at the 6-311G* DFT level, considering energies of the varying conformers, aromaticity and magnetic criteria. Of the four possible isomers, *out,out*-**72** was most stable by up to 7.50 kcal/mol (Figure 1.9). However, the cyclization energy of *out,in*-**78** is slightly lower at 5.29 kcal/mol compared to 5.95 kcal/mol. The high activation energies for bond formation from *in,out*-**75** and *in,in*-**81** make these isomers less likely participants in the reaction.

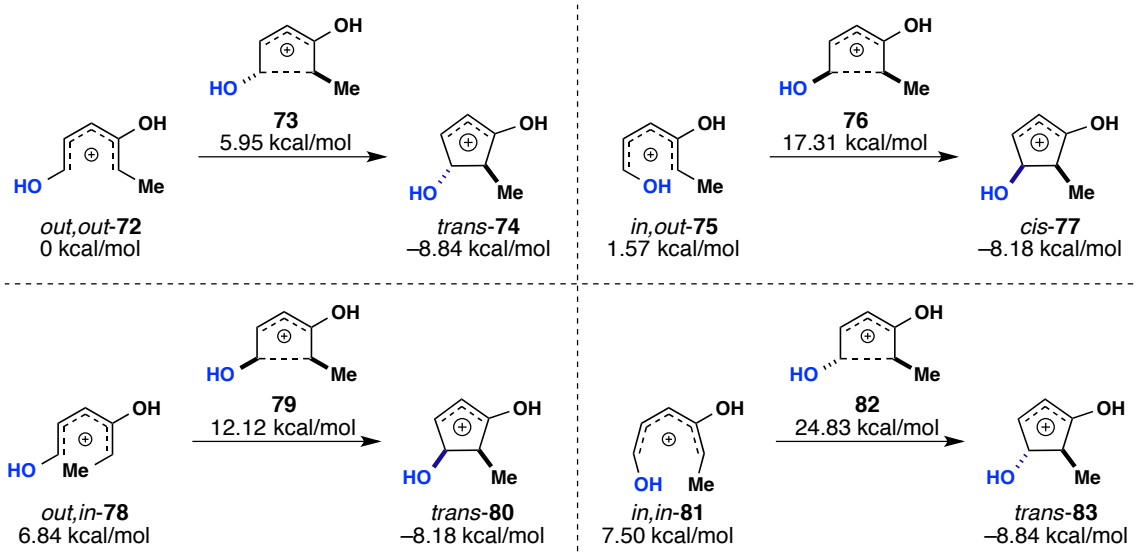


Figure 1.9. Possible isomers in the Piancatelli rearrangement and their energies.

The possibility of an aldol-type reaction was also considered, and was analyzed via the natural bond orbital (NBO) method. They found a significant charge separation at the termini of the system (**84**), which helps in lowering the energy of the electrocyclization (Figure 1.10). This facilitation of bond formation via charge separation is quite similar to the observed increase in reaction rates in Frontier's study of donor-acceptor Nazarov substrates (**24**).[24] The conclusion that the Piancatelli rearrangement proceeds via a 4π conrotatory electrocyclization via the *out,out*-isomer (**72**) is in complete agreement with the observed *trans*-selectivity reported by Piancatelli and others.

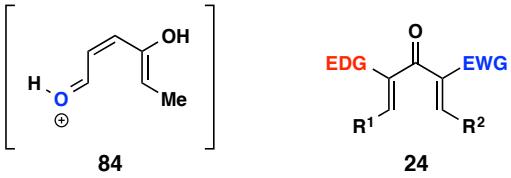


Figure 1.10. Charge separation in the Piancatelli rearrangement.

The simplicity and untapped potential of the Piancatelli rearrangement have served as the inspiration for the work presented within this thesis.

2. The Aza-Piancatelli Rearrangement

2.1. The Importance of 4-Aminocyclopentenones

The simplicity with which a densely functionalized small molecule can be accessed from a sustainable starting material via the Piancatelli rearrangement inspired our group to elaborate on the methodology by developing an aza variant of the reaction. The importance of nitrogen-containing molecules was briefly discussed in the introduction, but this point cannot be emphasized enough. A large majority of the world's top selling pharmaceuticals contain at least one carbon-nitrogen bond, and amine functional groups are widely represented in nature. However, nitrogen compounds are notoriously difficult to work with due to the basicity of the nitrogen, which is also the cause of many incompatibilities when metal catalysts are involved. Installing nitrogen functionalities is no easy task; doing so in a chemoselective, stereoselective or enantioselective manner can be a lengthy and downright daunting process.

The aminocyclopentane scaffold (**1**) is well represented in natural products and pharmaceutically active compounds with homoharringtonine (**3**), stemonamine (**4**), pactamycin (**2**), (–)-agelastatin A (**6**) and an hNK1 inhibitor (**7**) serving as illustrative examples (Figure 2.1.).

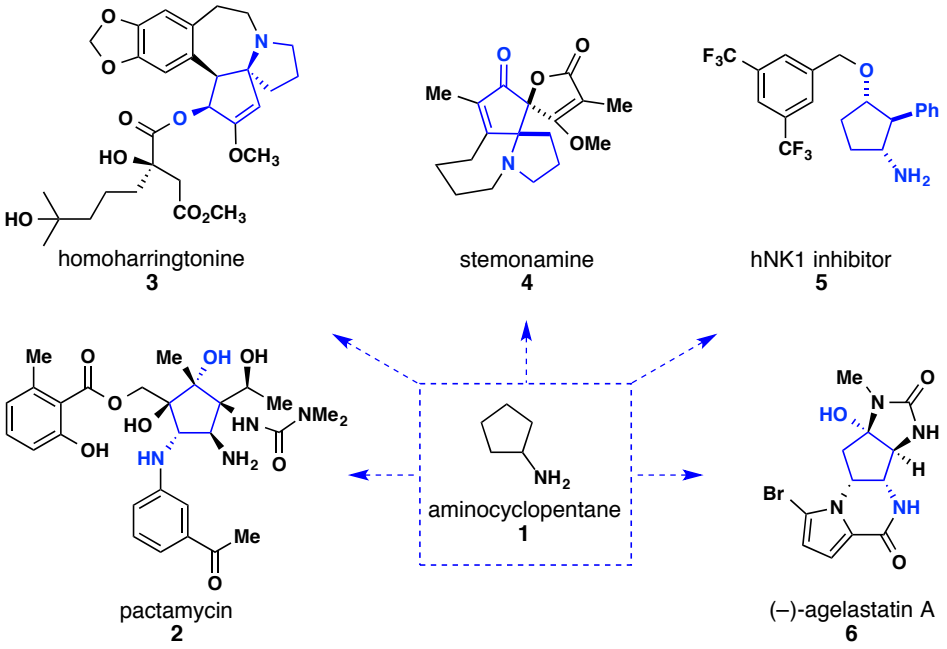
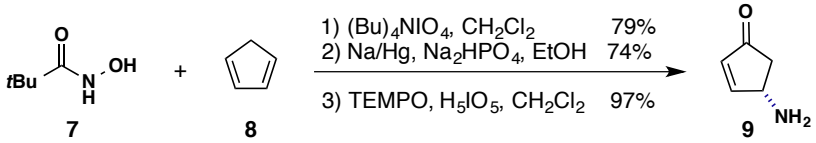


Figure 2.1. Natural products and biologically active cyclopentanes.

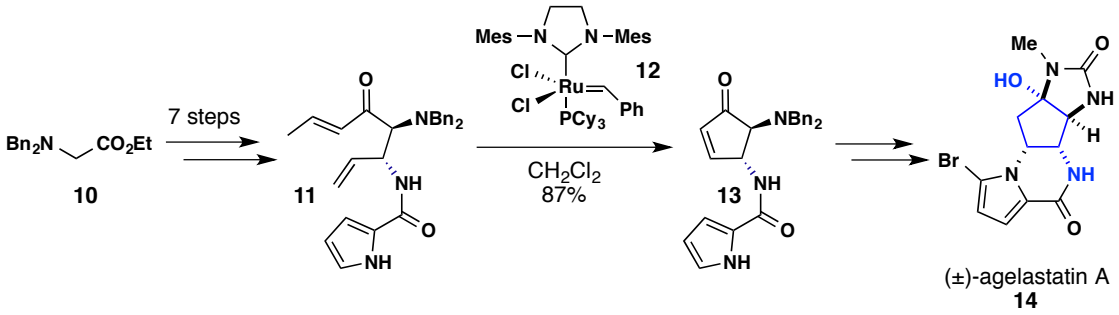
Methods to access this scaffold directly are scarce, forcing chemists to embark on elaborate synthetic journeys to generate aminocyclopentanes. Miller and Happe have reported methods for the formation of 4-aminocyclopentanes via nitroso hetero-Diels–Alder (HDA) reactions with cyclopentadienes (Scheme 2.1).[59–62] Cleavage of the N–O bond followed by oxidation provides access to 4-aminocyclopentenones (**9**). However, the synthesis of these products requires three forcing steps, is limited by the diene partner, and lacks substitution at the α-position.



Scheme 2.1. Happe's 4-aminocyclopentenone synthesis via the HDA.

Davis and co-workers developed a method to access 4-aminocyclopentenones from Davis' chiral sulfinimine via Grubbs metathesis.[63] The group then applied their

methodology to the total synthesis of (–)-agelastatin A (**14**) (Scheme 2.2).[64] Although the ring closing metathesis (RCM) reaction could be considered a step toward green chemistry (*vide supra*), the seven step synthesis required to access the precursor is less than ideal.



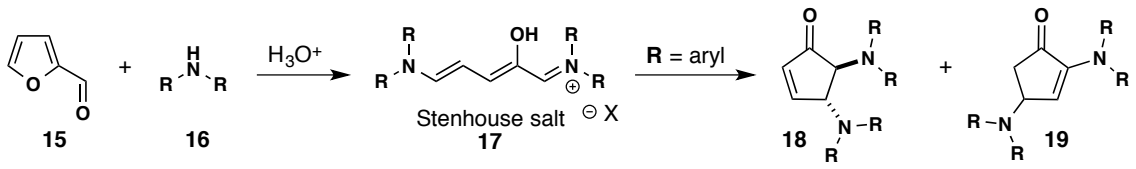
Scheme 2.2. Access to 4-aminocyclopentenones via Grubbs metathesis.

Additional notable progress in the field has been accomplished by Johnson,[65–67] Miller[61,62] and Batey[40] and will be discussed in later parts of this thesis.

2.2. Rearrangements of Furan Derivatives with Amines

Examples of rearrangements of furfural and its derivatives to substituted aminocyclopentenones are scarce in the literature. Of course the limited but significant examples make this an exciting area of research.

The path to the formation of 4,5-diaminocyclopentenones takes us all the way back to 1850, where Dr. J. Stenhouse described the formation of highly colored salts (**17**) from a 2:1 condensation of fufural (**15**) with amines (**16**) in the presence of Brønsted acids (Scheme 2.3).[68] The chemistry of these highly colored substances was further investigated by Schiff[69,70] and Zincke.[71] It wasn't until almost a century later that the real value of these salts in terms of aminocyclopentanes was demonstrated by Lewis and co-workers who showed that 4,5-diaminocyclopentenones (**18**) could be generated in low yield from the reaction of furfural and anilines (Scheme 2.3).[72,73]



Scheme 2.3. Formation of Stenhouse salts and 4,5-diaminocyclopentenones from furfural.

The low yields are likely due to the harsh conditions used for these transformations, as well as the formation of the 2,4-diaminocyclopentenone (**19**). Batey and Li set out to improve on Lewis' efforts to develop a mild and efficient method for the synthesis of *trans*-substituted diaminocyclopentenones (**21**) with hopes that this methodology would provide access to the *trans*-substituted-4,5-diaminocyclopentane unit in (–)-agelastatin A (**6**, Figure 2.1.).[40] A screen of Lewis acid catalysts led them to explore rare earth triflates ($RE(OTf)_3$) for the rearrangement. Figure 2.2 summarizes their results when using either scandium trifluoromethansulfonate ($Sc(OTf)_3$) or dysprosium trifluoromethansulfonate ($Dy(OTf)_3$). Dysprosium and other $RE(OTf)_3$ have many desirable properties compared to traditional Lewis acids. For one, they are both air and moisture stable and non-toxic, allowing for easy handling. Additionally, rare earth triflates are relatively oxophilic and can actively catalyze reactions in the presence of Lewis basic amines. The properties and merits of dysprosium and its use in synthesis are discussed in detail in Chapter 3 of this thesis.

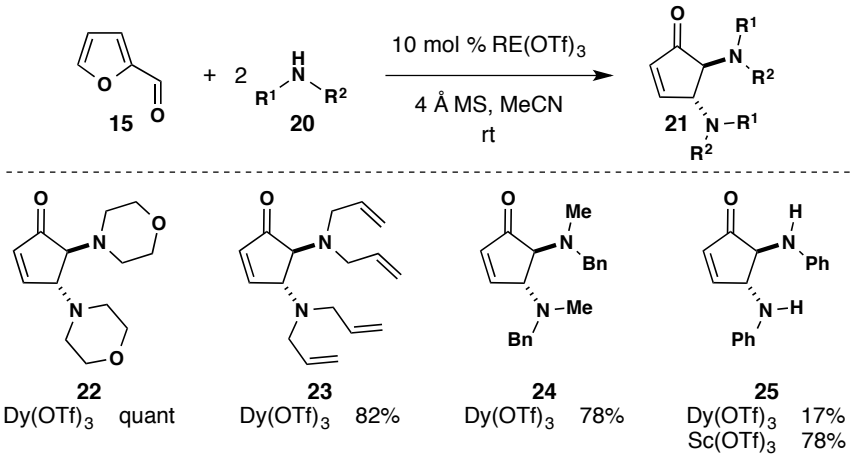
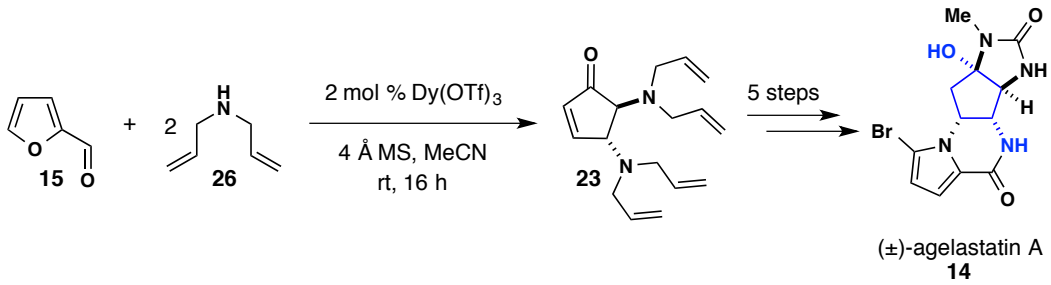


Figure 2.2. Scope of Batey's 4,5-diaminocyclopentenone synthesis.

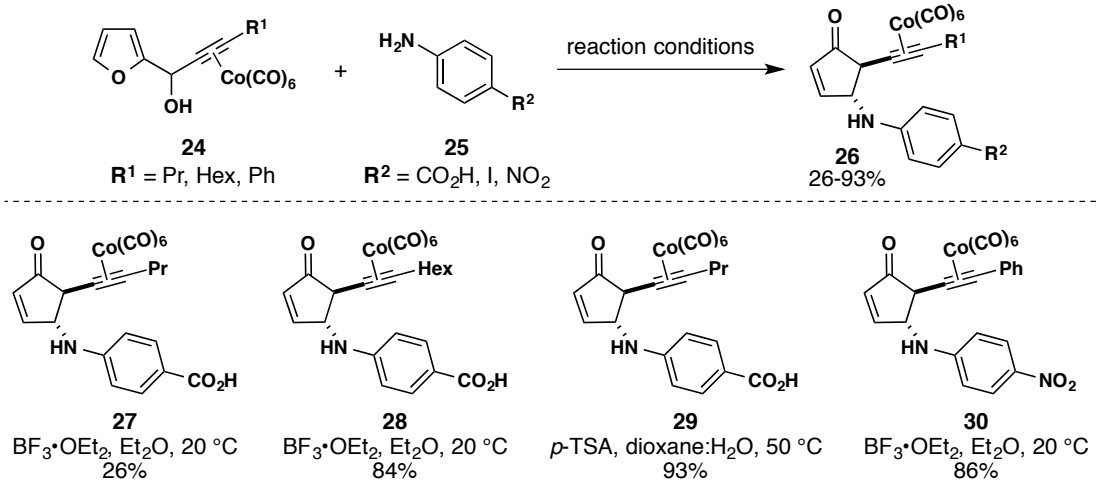
The proposed mechanism for the reaction is thought to proceed via a 4π electrocyclization analogous to the Piancatelli rearrangement, accounting for the observed *trans*-selectivity. Six years after their initial development of the rearrangement, Batey and Duspara employed the rearrangement as the key transformation in their elegant six step total synthesis of (±)-agelastatin A (**14**) (Scheme 2.4).[74] It is remarkable how quickly the desired *trans*-4,5-diaminocyclopentenone (**23**) can be accessed using Batey's method compared to Davis' elaborate effort to generate the requisite precursor (**11**) for the key RCM reaction (Scheme 2.2).



Scheme 2.4. Batey's synthesis of (±)-agelastatin A.

Comparatively much less work has been completed in terms of the rearrangement of furylcarbinols. Throughout his extensive investigations of the rearrangements of furfuryl

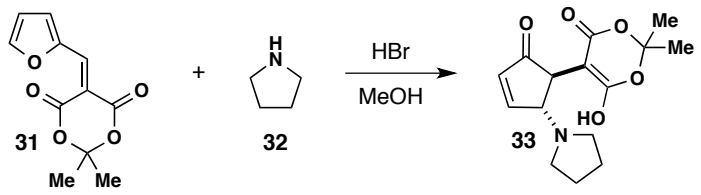
alcohols, Piancatelli never strayed away from the hydroxyl group as the nucleophile. Denisov and co-workers reported the only example of a Piancatelli rearrangement with an amine in 1993. The conditions for the rearrangement were similar to those developed by Piancatelli, requiring stoichiometric amounts of acid, such as *p*-TSA or $BF_3 \bullet OEt_2$.[75] Aside from the relatively forcing conditions, the range of nucleophiles for the transformation was limited to only three electron deficient *para*-substituted anilines (**25**) and specialized cobaltacene-protected alkynyl furylcarbinols (**24**) (Scheme 2.5). Reaction conditions for the rearrangement were adjusted from substrate to substrate, and yields for the reaction were variable, ranging from poor (26%) to excellent (93%).



Scheme 2.5. Scope of Denisov's aza-Piancatelli rearrangement.

In addition to the report by Denisov and co-workers, we were intrigued by a publication by Safar and co-workers that described the rearrangement of furans containing a Meldrum's acid unit (**31**) to cyclopentenones **33** when treated with HBr in the presence of cyclic amines, such as pyrrolidine (**32**) (Scheme 2.6).[76] This scaffold has since been applied to the development of a new class of photoswitch from donor-acceptor Stenhouse adducts

(DASAs) for applications in polymer and materials chemistry in a collaboration between the Read de Alaniz and Hawker groups.[77]

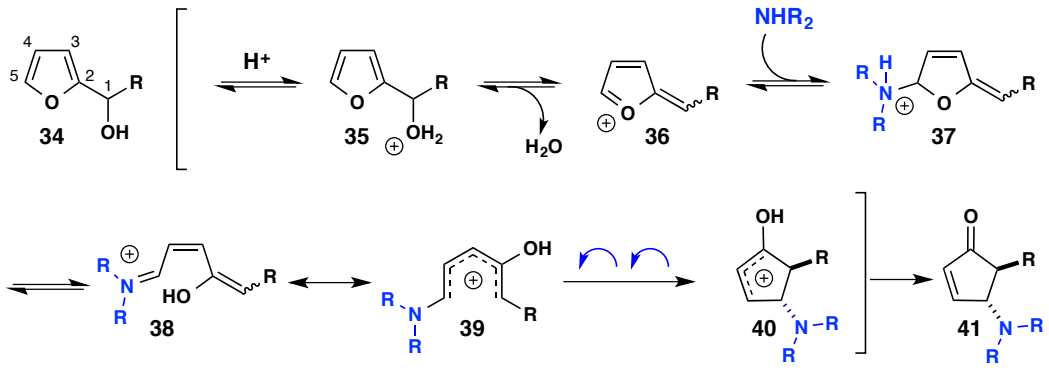


Scheme 2.6. Synthesis of 4-aminocyclopentenones from a Meldrum's acid furan derivative.

The examples detailed above demonstrate the ability of amines to participate in rearrangements similar to the Piancatelli rearrangement with water. Entering this research area, it was our goal to develop a simple and general method for the formation of 4-aminocyclopentenones directly from a cheap sustainable starting material under mild conditions.

2.3. The Aza-Piancatelli Rearrangement

Driven by the need for simple ways to access aminocyclopentenes, our group decided to focus on developing a Piancatelli rearrangement with amines. We hypothesized that judicious choice of a Lewis acid capable of activating the furylcarbinol (**34**) in the presence of the Lewis basic amine nucleophile would initiate the cascade reaction to form *trans*-substituted 4-aminocyclopentenones (**41**) (Scheme 2.7).



Scheme 2.7. Proposed mechanism of the aza-Piancatelli rearrangement.

Initial studies were performed with phenyl furylcarbinol **43**, prepared via a simple Grignard addition (Scheme 2.11, step 1), and commercially available *p*-iodoaniline in acetonitrile (MeCN). Based on Batey's success with rare earth triflate catalysis in the presence of amines, we commenced our studies with these catalysts. Satisfyingly, we found that either $Dy(OTf)_3$ or $Sc(OTf)_3$ catalyzed the reaction to cleanly give the desired *trans*-substituted 4-aminocyclopentenone **42** in excellent yield (entries 1-3, Table 2.1).[78] Other solvents were explored, but reactions in tetrahydrofuran (THF), methylene chloride or toluene were slower and resulted in some undesired side reactions, and MeCN gave the best results overall. Coupling constants for the enone peaks were consistent with products exhibiting a *trans* relationship between the amine and R-group, a relationship that was later confirmed by single-crystal X-Ray crystallography (Figure 2.3), leading us to conclude that the reaction does indeed go through a 4π conrotatory electrocyclization as described in the proposed mechanism (Scheme 2.7).

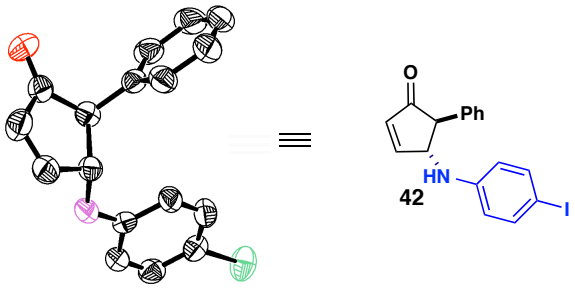
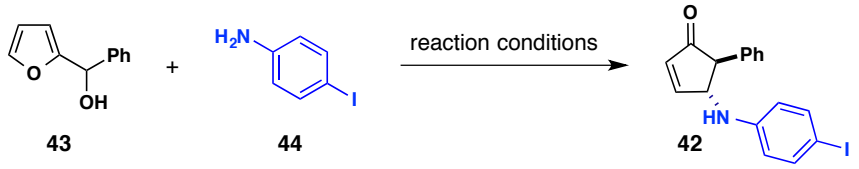


Figure 2.3. ORTEP drawing of the crystal structure of 4-aminocyclopentenone **42** with 50% thermal ellipsoids. CCDC 769123.

Table 2.1. Screen of reaction conditions for the aza-Piancatelli rearrangement.[a]



43 44 42

Entry	Catalyst	Temp (°C)	Time	Yield (%)[c]
1	5 mol % $Sc(OTf)_3$	40	3 h	83
2	5 mol % $Dy(OTf)_3$	40	2 h	79
3	**5 mol % $Dy(OTf)_3$**	**80**	**30 min**	**92**
4	5 mol % HOTf	80	30 min	62
5[b]	5 mol % HOTf 100 mol % K_2CO_3	80	4 h	0
6	5 mol % $Dy(OTf)_3$ 100 mol % K_2CO_3	80	1 h	93

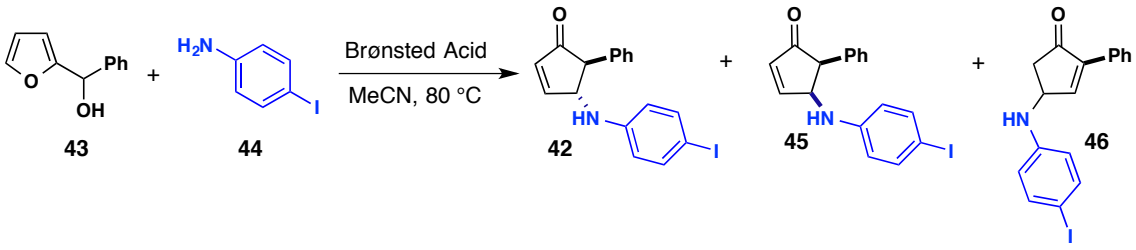
[a] All reactions were performed in MeCN. [b] The starting material was recovered from the reaction. [c] Isolated yields.

Because it is known that triflic acid (HOTf) can be released in reactions with rare earth triflates ($RE(OTf)_3$),[79] we performed a series of control experiments to determine if this was the case with our reaction. Although 5 mol % HOTf was an effective catalyst for the rearrangement (Table 2.1, entry 4), the reaction was much cleaner with $Dy(OTf)_3$. Addition of one equivalent (equiv) of potassium carbonate (K_2CO_3) completely shut down the reaction with HOTf (Table 2.1, entry 5) resulting in complete recovery of starting materials, while addition of one equiv K_2CO_3 merely slowed down the reaction with $Dy(OTf)_3$ without affecting the yield of the reaction (Table 2.1, entry 6).

A screen of other protic acids revealed a clear effect of the pKa on the rearrangement. Hydrochloric acid and sulfuric acid catalyze the rearrangement, but the reactions are not very clean and the strong acids can result in loss of the *trans* stereochemistry (**45**) and further rearrangement to the more highly substituted cyclopentenone **46** (entries 1-3, Table 2.2). Camphorsulfonic acid ((±)-CSA) and trifluoroacetic acid (TFA) are excellent catalysts

for the rearrangement, resulting in only the desired product in 84% and 90% yield, respectively (entries 4 and 5, Table 2.2). The pKa of acetic acid (4.75 compared to –0.25 for TFA) was determined to be too high to effectively activate the furylcarbinol, and only starting material was recovered from this reaction (entry 6, Table 2.2).

Table 2.2. Effect of pKa on the aza-Piancatelli rearrangement.



Entry	Catalyst	pKa	Time	Yield (42:45:46) (%)
1	HCl	–8	1 h	93:6:0
2[a]	HCl	–8	2 weeks	N/A
3	H_2SO_4	–3	48 h	68:0:14
4	(±)-CSA	–1	8 h	84:0:0
5	TFA	–0.25	1 h	90:0:0
6[b]	AcOH	4.76	>72 h	N/A

[a] Reaction performed at rt. [b] The starting material was recovered from the reaction.

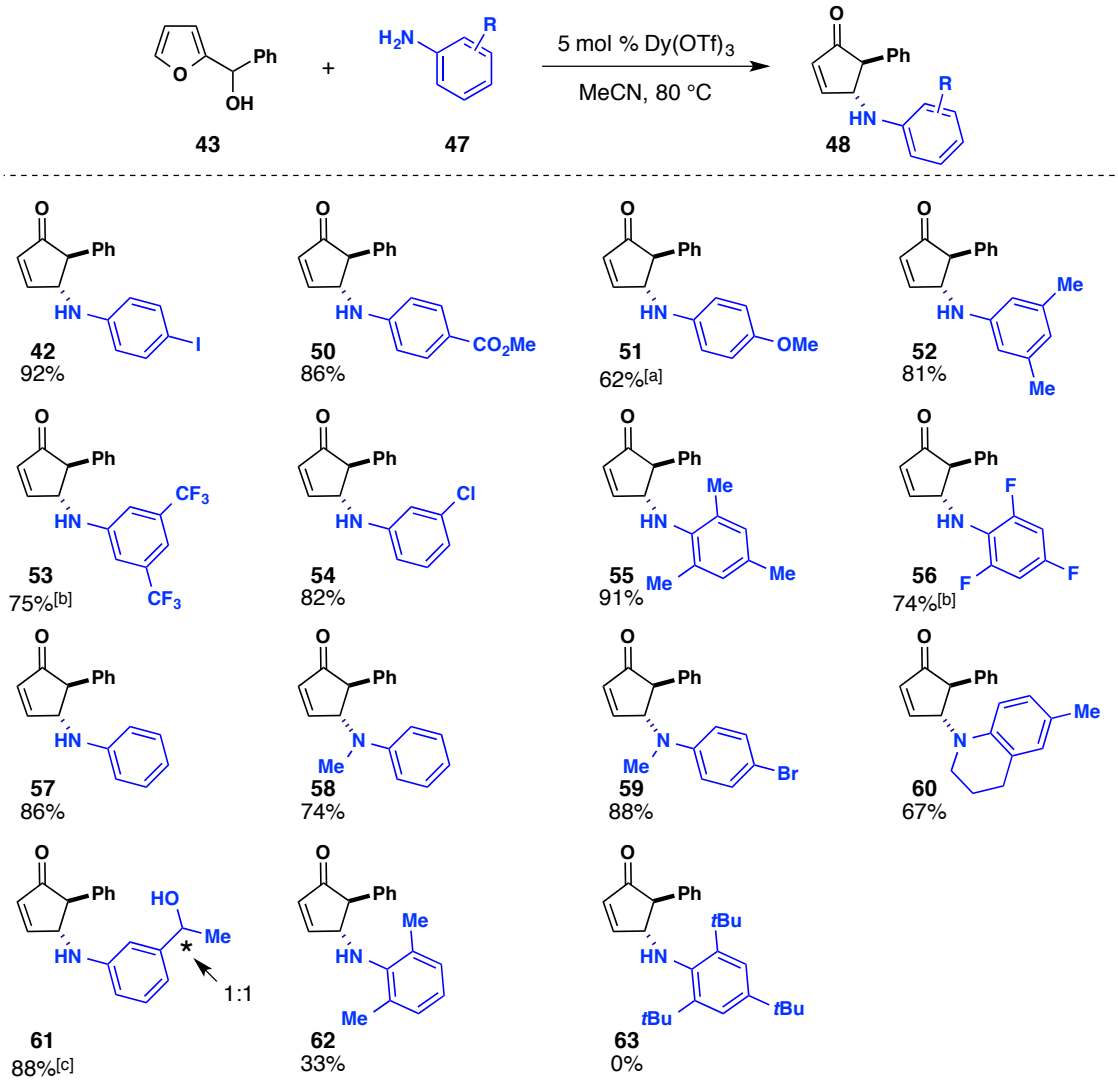
Other rare earth triflates ($Yb(OTf)_3$, $La(OTf)_3$, $Ce(OTf)_3$, $Nd(OTf)_3$) have been tested and were shown to be effective catalysts, but we chose to focus our efforts on reactions with dysprosium.

2.4. The Scope of the aza-Piancatelli rearrangement

Having established effective reaction conditions for the rearrangement of phenyl furylcarbinol **43** with *p*-iodoaniline (5 mol % $Dy(OTf)_3$, MeCN, 80 °C), we were ready to develop the scope of the aza-Piancatelli rearrangement. Initial explorations focused on the range of anilines able to participate in the cascade. The results of these investigations are summarized in Table 2.3. A variety of *ortho*-, *meta*-, and *para*-substituted anilines

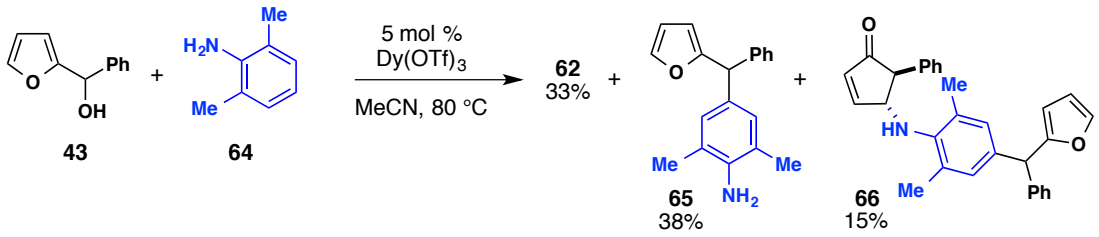
participated in the rearrangement, including electron rich (**51**) and electron poor anilines (**51**). Even sterically hindered 2,4,6-trimethylaniline gave the desired products in excellent yield (**55**, 91%). As may be expected, when bulkier groups are placed next to nitrogen, the reactivity is eventually stunted, and thus extremely sterically hindered 2,4,6-tri-*tert*butylaniline (**63**) did not participate in the reaction, resulting in recovery of starting material. Disubstituted secondary anilines also generated the desired tertiary amino-substituted cyclopentenones (**58**, **59**, and **60**). In general, we observed that reactions with electron rich anilines proceeded at a slower rate than electron poor anilines, presumably the increased basicity leads to competitive binding of the dysprosium catalyst.

Table 2.3. Scope of the aza-Piancatelli rearrangement with phenyl furylcarbinol.



[a] The reaction was performed with 20 mol % Dy(OTf)$_3$. [b] The reaction was performed with 3 equiv amine. [c] Formed as a 1:1 ratio of diastereomers.

The reactions were generally clean, and no rearrangement to the more highly substituted cyclopentenone was observed under Dy(OTf)$_3$ catalyzed conditions. However, in the case of sterically hindered, electron rich 2,6-dimethylaniline, the desired product (**62**) was formed in only 33%, while two additional products were observed. The side products **65** and **66** were formed in 38% and 15%, respectively, and are results of Friedel–Crafts alkylation (Scheme 2.8).

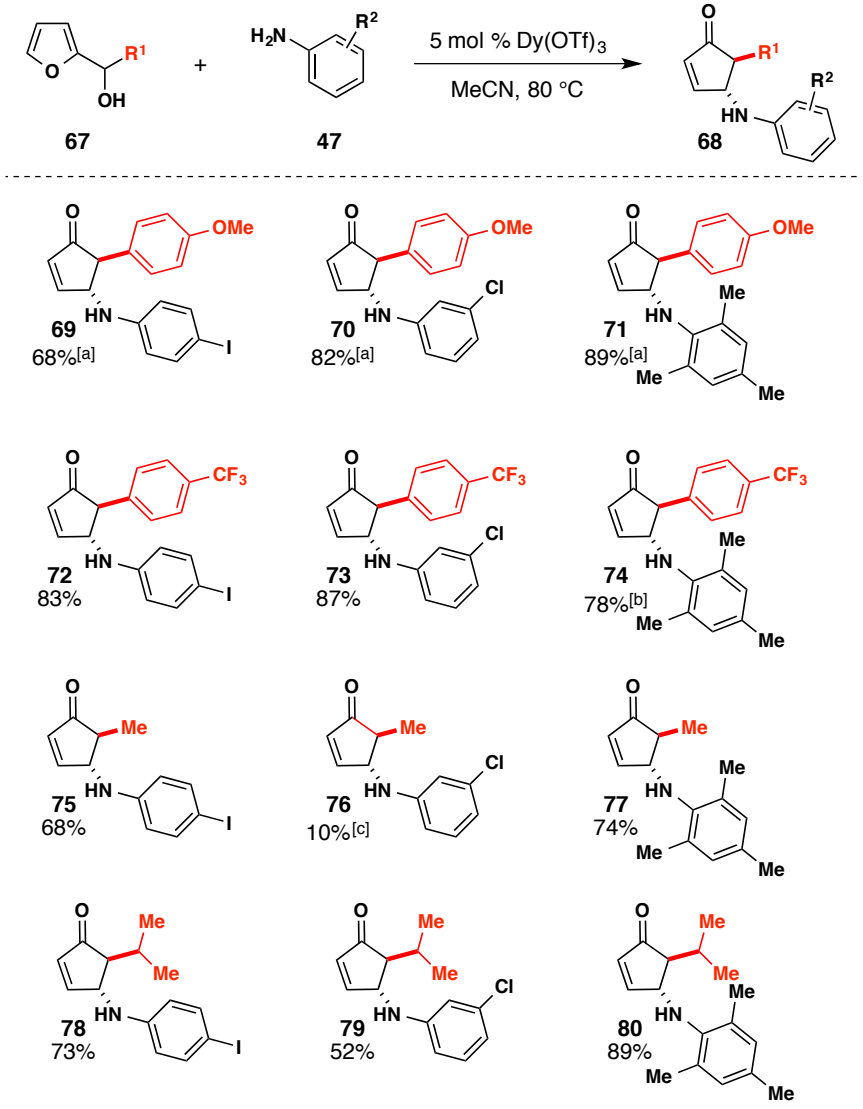


Scheme 2.8. Friedel–Crafts side reactions with electron rich hindered anilines.

Having determined that a wide range of anilines will participate in the rearrangement, we set out to evaluate the scope of furylcarbinols. Experiments with electron rich *p*-methoxyphenyl furylcarbinol or electron poor *p*-trifluoromethylphenyl furylcarbinol proceeded cleanly to give the desired products with a variety of aniline partners (Table 2.4, **69**-**74**). Reactions with electron rich *p*-methoxyphenyl furylcarbinol were much faster compared to unactivated substrates, presumably because the alcohol was more prone to activation; however we also found that this furylcarbinol was much less stable than other furylcarbinols and had to be stored in the freezer. Additionally, extended exposure to light was avoided to limit decomposition of the starting material. Because of these factors, reactions with *p*-methoxyphenyl furylcarbinol were conducted at rt. Reactions with *p*-trifluoromethylphenyl furylcarbinol were much slower compared to phenyl furylcarbinol, and in the case of hindered 2,4,6-trimethylaniline, this necessitated the use of 20 mol % $Dy(OTf)_3$ to generate the **74** at a reasonable rate.

We were pleased to find that furylcarbinols with methyl or isopropyl groups also rearrange to give cyclopentenones **75**-**80** (Table 2.4). The decrease in yields with alkyl furylcarbinols can be attributed to starting materials that are less stable compared to phenyl furylcarbinol. In the rearrangement of methyl furylcarbinol with *m*-chloroaniline (**76**), the exceptionally low yield was attributed to the formation of Friedel–Crafts side products.[80–82]

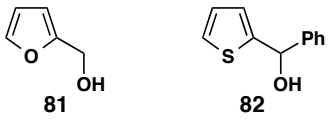
Table 2.4. Scope of the aza-Piancatelli rearrangement with different furylcarbinols.



[a] The reaction was performed at rt. [b] The reaction was performed with 10 mol % $Dy(OTf)_3$. [c] Friedel–Crafts alkylation products were observed.

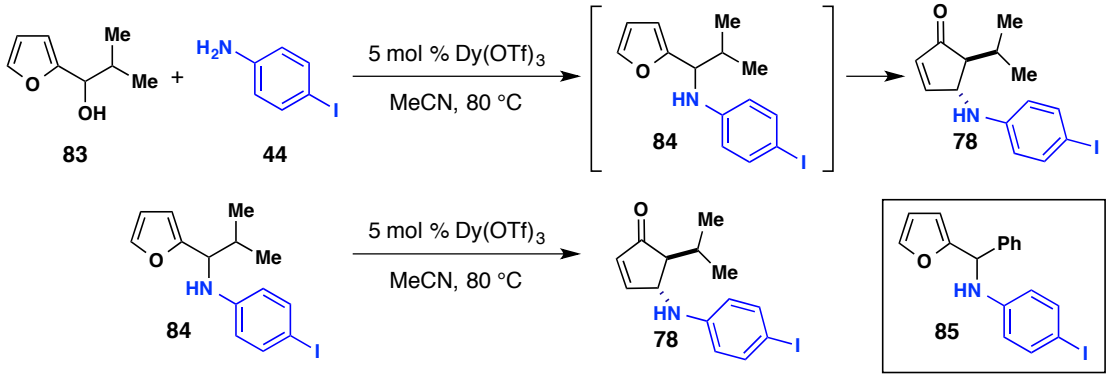
We also examined the rearrangement with unsubstituted furylcarbinol **81**, but found that the rearrangement did not take place (Scheme 2.9). We speculated that this was due to the lack of stabilization of the carbocation upon loss of water. The thiophene analog of phenylfurylcarbinol, **82**, was also subjected to the reaction conditions, but did not rearrange,

presumably due to the increased aromatic stabilization energy of thiophene (see Chapter 1.5).



Scheme 2.9. Substrates that did not undergo the aza-Piancatelli rearrangement.

During our studies on the rearrangement of isopropyl furylcarbinol to **83** we became intrigued by a transient product, which was observed by thin layer chromatography (TLC). We chose to isolate this product and found that it was the product of amine substitution at the 1-position of the furylcarbinol (**84**) (Scheme 2.10). Resubjecting the substitution product **84** to the reaction conditions led to complete conversion to the desired cyclopentenone **78**. Further investigations revealed that this substitution product forms during the first 3 to 5 minutes of the reaction between phenyl furylcarbinol and *p*-iodoaniline (**85**), but is not observable after that point. Due to the short lifetime of this intermediate, it is most likely an off-cycle product that re-enters the productive pathway upon loss of the aniline and formation of the oxocarbenium (**36**, Scheme 2.7). It should be noted that formation of this substitution product was more prominent in less polar solvents such as CH_2Cl_2 and THF.



Scheme 2.10. Formation of a substitution product during the reaction.

Overall, we found that the rearrangement was general both in terms of the anilines and furylcarbinols that can be employed for the dysprosium triflate catalyzed aza-Piancatelli rearrangement.

2.5. Synthesis of an hNK1 Inhibitor

With robust reaction conditions and a solid reaction scope in hand, we were excited to apply the rearrangement to the synthesis of a small molecule with interesting biological activity. A 2006 structure-activity relationship (SAR) study by chemists at Merck investigated the 1,2-*trans*-2,3-*trans*-cyclopentane scaffold (**86**) as a human neurokinin 1 (hNK1) antagonist (Figure 2.4).[83,84] Their studies found that the hNK1 inhibition with these cyclopentanes was comparable to that of Aprepitant (**87**), an FDA approved drug for the treatment of chemotherapy induced nausea and vomiting.

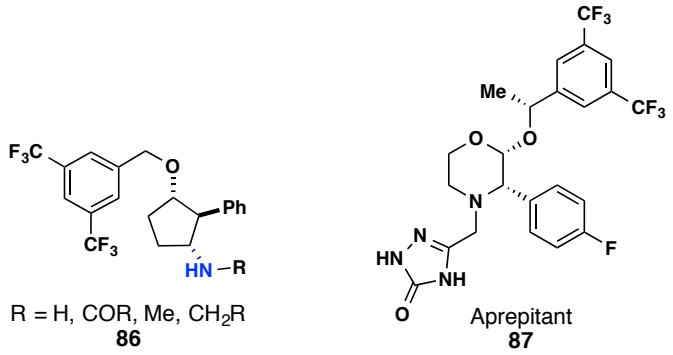
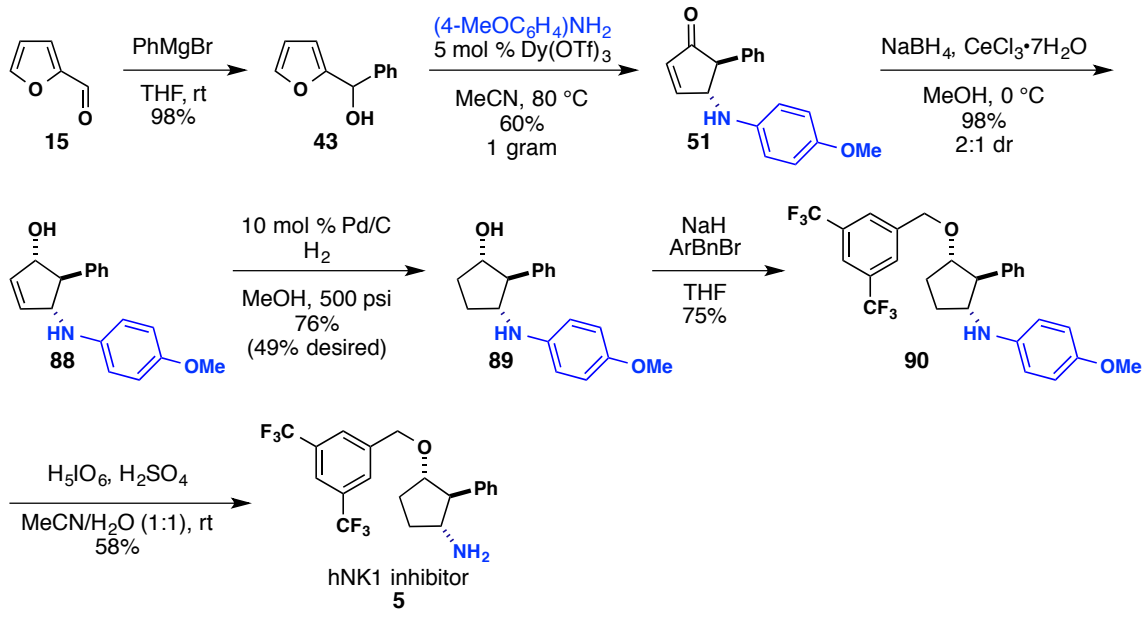


Figure 2.4. Structures of SAR study cylopentanes and Aprepitant.

We commenced our synthetic efforts toward the synthesis of hNK1 inhibitor **5**, confident that our *trans*-substituted aminocyclopentenone scaffold could serve as the key intermediate in the synthesis.[78] Phenyl furylcarbinol was easily prepared on a 10 gram scale via a simple Grignard addition to furfural, and we were pleased to demonstrate that the aza-Piancatelli rearrangement with *para*-methoxyphenyl (PMP) aniline could be performed on a 1 gram scale to provide **51** (Scheme 2.11). Although the subsequent Luche reduction of the ketone

was only moderately selective (2:1 dr), the major product did display the desired 1,2-*trans*-2,3-*trans* stereochemistry (**88**). Based on more recent results with Luche typed reductions, I am confident that this selectivity could be improved (*vide infra*). Alkene reduction to the cyclopentane (**89**) required rather forcing hydrogenation conditions. However, a more thorough investigation of hydrogenation catalysts may reveal that milder conditions would suffice. The reduction was followed by chemoselective *O*-alkylation. Our alkylation studies showed that formation of the *N*-alkylated product could occur, but use of excess sodium hydride resulted in exclusive formation of the *O*-alkylation product **90**. Oxidative removal of the PMP group proved to be quite challenging. Standard conditions using ceric ammonium nitrate (CAN) resulted in decomposition of the product or recovery of the starting material.[85,86] After many trials and tribulations, we were delighted to discover that treatment of **90** with periodic acid (H_5IO_6) and H_2SO_4 generated the desired primary amine, completing the synthesis of the desired hNK1 inhibitor **5** in only 6 steps from furfural (Scheme 2.11).[87] Comparing this short synthesis to the 20 steps it took to prepare the hNK1 inhibitors described in the study by Merck truly highlights the value and potential of the aza-Piancatelli for applications in medicinal chemistry and total synthesis.



Scheme 2.11. Synthesis of an hNK1 inhibitor.

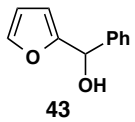
2.6. Experimental Procedures

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Merck KGA). ^{1}H NMR spectra were recorded on Varian spectrometers (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 MHz).

Data for ^{13}C NMR spectra are reported as follows: shift (δ ppm), multiplicity and coupling constant (Hz). IR spectra were recorded on a Jasco FT/IR 4100 and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra and X-Ray analysis were obtained from the UC Santa Barbara Mass Spectrometry and X-Ray Facilities.

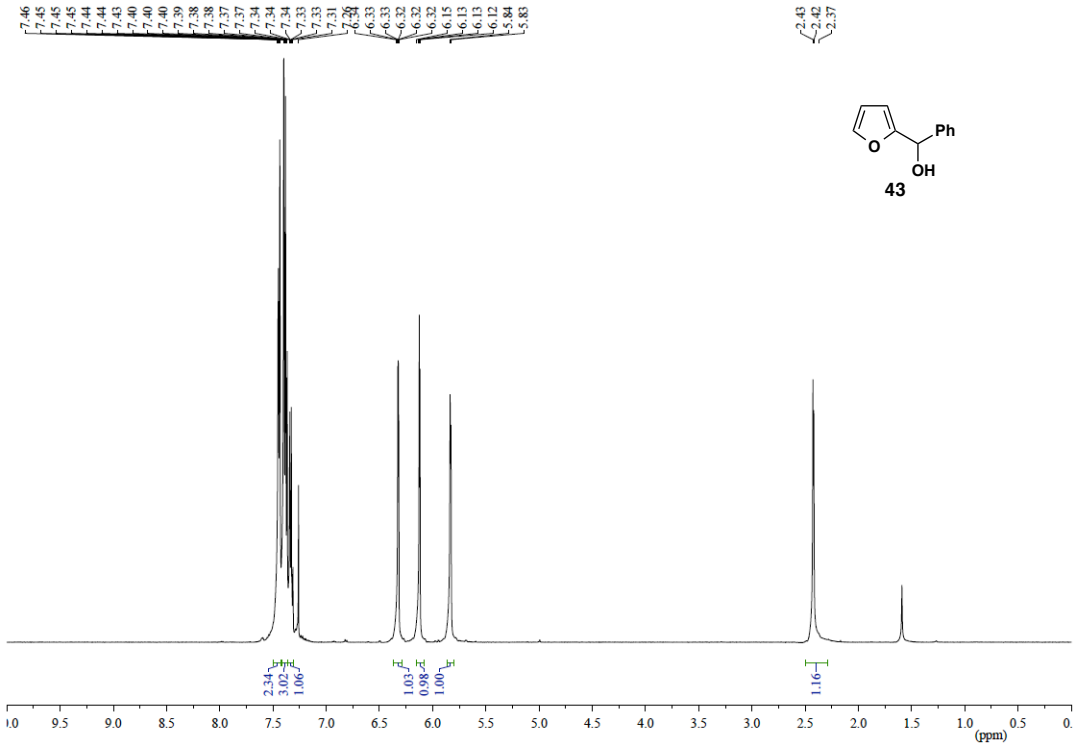
Furylcarbinols **43**, **92**, **83**, **105** were prepared according to literature precedent by reacting furfural with the corresponding Grignard reagent.[88] Furylcarbinol **106** was used as received. The crystal structure data for 4-((4-iodophenyl)amino)-5-phenylcyclopent-2-enone **42** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif CCDC 769123.

Experimental Procedures.



43

Furan-2-yl(phenyl)methanol (43): Light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 – 7.43 (m, 2H), 7.42 – 7.36 (m, 3H), 7.36 – 7.30 (m, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 5.83 (d, *J* = 4.0 Hz, 1H), 2.42 (d, *J* = 4.3 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.1, 142.7, 140.9, 128.6, 128.2, 126.7, 110.4, 107.6, 70.3 ppm; **IR** (thin film) 3362, 3063, 3031, 2897, 1957, 1888, 1810, 1602, 1492, 1452, 1141, 1007 cm^{-1}; **MS** (EI^+) *m/z* 174.0685 (174.0681 calcd for $C_{11}H_{10}O_2^+$ $[M]^+$).


7.46
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5.83
2.43
2.42
2.37
Ph
O
OH
43
2.34
3.02
1.06
1.03
0.98
1.00
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1.0
9.5
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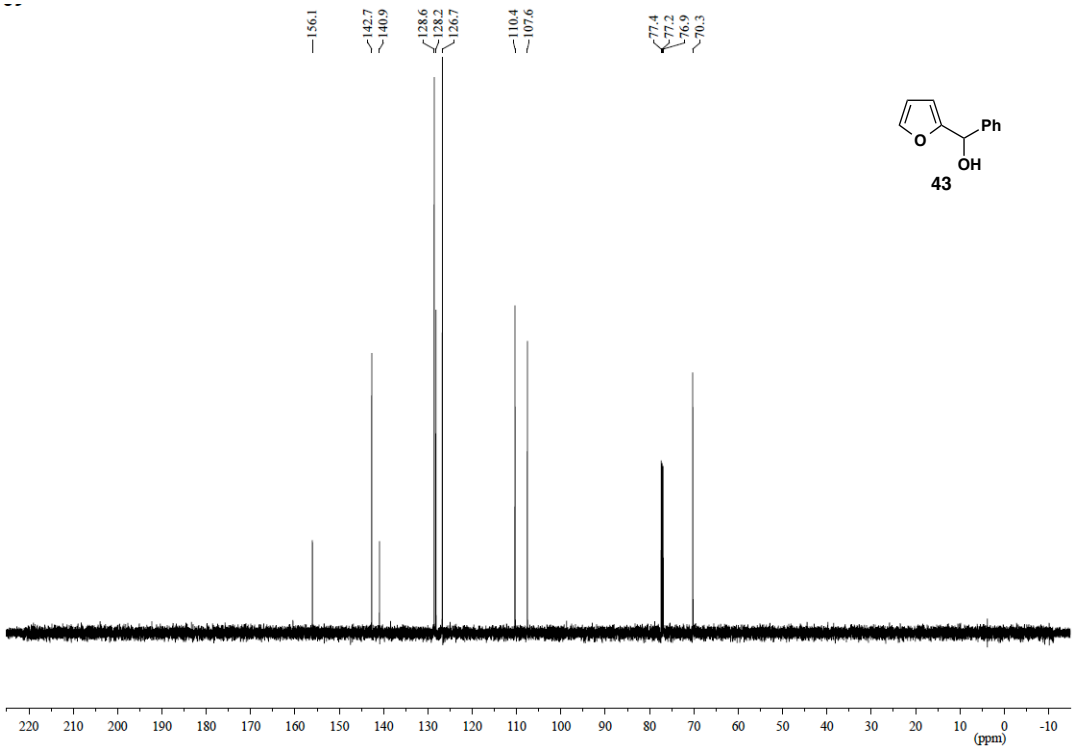
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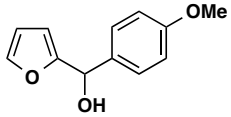
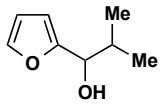

OMe
O
OH

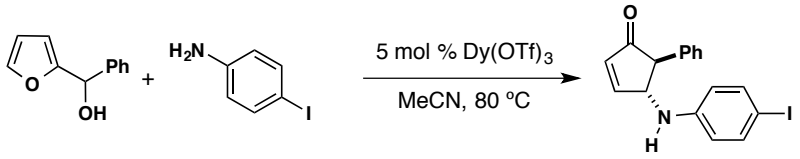
92

Furan-2-yl(4-methoxyphenyl)methanol (92): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 0.8 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.31 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 5.76 (s, 1H), 3.80 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.5, 156.3, 142.5, 133.2, 128.1, 113.9, 110.3, 107.3, 69.9, 55.4 ppm; **IR** (thin film) 3402, 3001, 2957, 2935, 2910, 2837, 1610, 1586, 1510 cm^{-1}; **MS** (EI) *m/z* 204.0776 (204.0786 calcd for $C_{12}H_{12}O_3^+$ $[M]^+$).



83

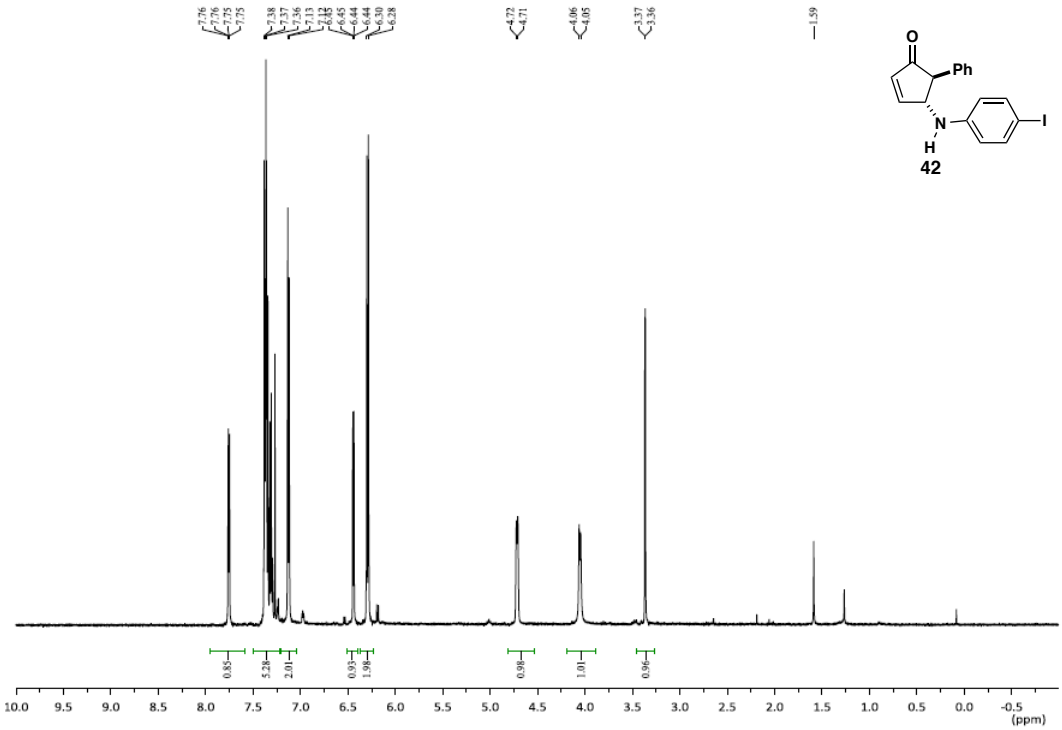
1-(Furan-2-yl)-2-methylpropan-1-ol (83): Yellow oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 (d, *J* = 3.2 Hz, 1H), 4.38 (d, *J* = 7.0 Hz, 1H), 2.11 (h, *J* = 6.8 Hz, 1H), 1.84 (s, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.3, 141.8, 110.2, 106.6, 73.7, 33.5, 18.9, 18.4 ppm; **IR** (thin film) 3392, 2961, 2933, 2873, 1665, 1505, 1468 cm^{-1}; **MS** (EI) *m/z* 140.0840 (140.0837 calcd for $C_8H_{12}O_2^+$ $[M]^+$).

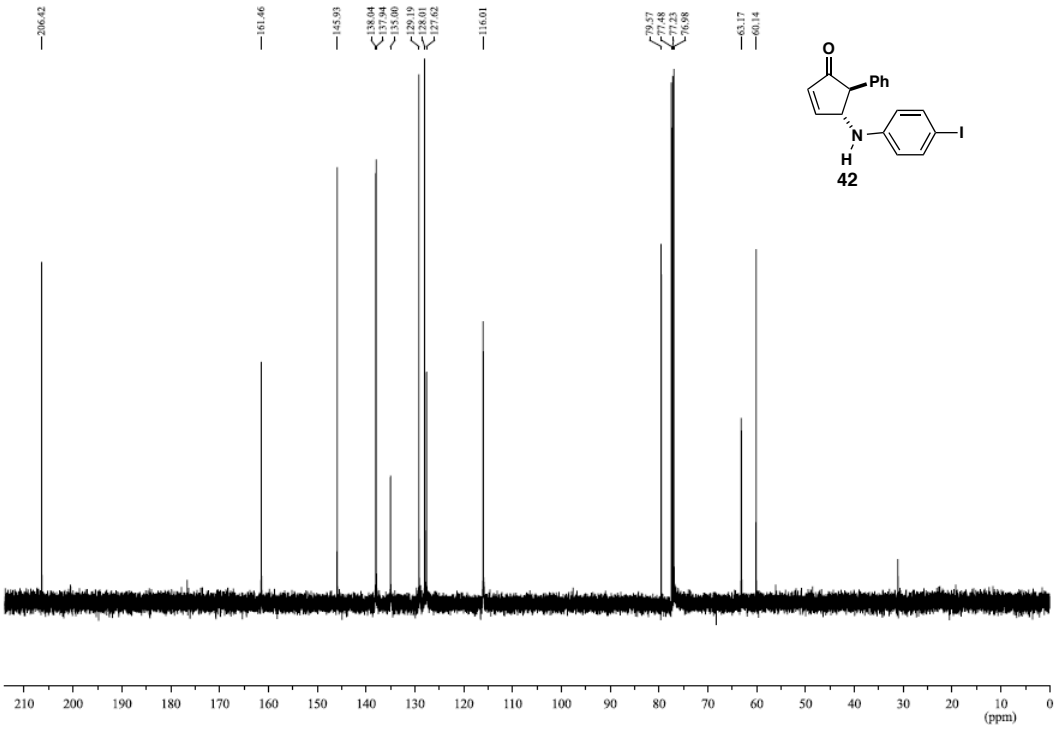


43 **44** **42**

4-((4-iodophenyl)amino)-5-phenylcyclopent-2-enone (42): According to the general procedure $Dy(OTf)_3$ (23 mg, 0.038 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (128 mg, 0.74 mmol, 1 equiv) and 4-iodoaniline **44** (162 mg, 0.74 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 30 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium

bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **42** (255 mg, 92%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.40 – 7.28 (m, 5H), 7.15 – 7.09 (m, 2H), 6.40 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.27 (dddd, *J* = 9.8, 2.0, 2.0, 2.0 Hz, 2H), 4.69 (dd, *J* = 8.2, 1.7 Hz, 1H), 4.19 (d, *J* = 8.3 Hz, 1H), 3.35 (d, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 161.5, 145.9, 138.0, 137.9, 135.0, 129.2, 128.0, 127.6, 116.0, 79.6, 63.2, 60.1 ppm; IR (thin film) 3776, 3026, 1704, 1588, 1496, 1316 cm^{-1}; HRMS (ESI) *m/z* 398.0022 (398.0012 calcd for $C_{17}H_{14}INONa^+$ [M + Na]$^+$).

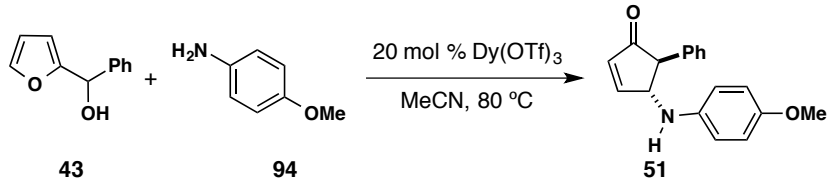




43 93 50

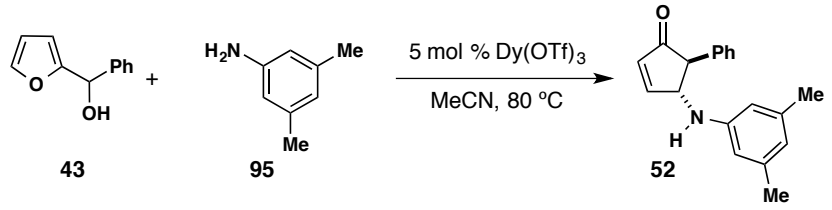
Methyl 4-((4-oxo-5-phenylcyclopent-2-en-1-yl)amino)benzoate (50): According to the general procedure $Dy(OTf)_3$ (17 mg, 0.028 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (97 mg, 0.56 mmol, 1 equiv) and methyl 4-aminobenzoate **93** (84 mg, 0.56 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **50** (148 mg, 86%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 2H), 7.75 (dd, J = 5.7, 2.3 Hz, 1H), 7.41 – 7.29 (m,

3H), 7.16 – 7.10 (m, 2H), 6.49 – 6.42 (m, 3H), 4.82 (dddd, J = 8.1, 2.2, 2.2, 2.2 Hz, 1H), 4.63 (d, J = 8.3 Hz, 1H), 3.84 (s, 3H), 3.39 (d, J = 2.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.2, 167.2, 161.0, 150.3, 137.8, 135.3, 131.7, 129.3, 128.1, 127.8, 119.8, 112.6, 62.8, 60.3, 51.8 ppm; IR (thin film) 3359, 3023, 2950, 1705, 1604, 1280 cm^{-1}; HRMS (ESI) *m/z* 330.1106 (330.1101 calcd for $C_{19}H_{17}NO_3Na^+$ $[M + Na]^+$).



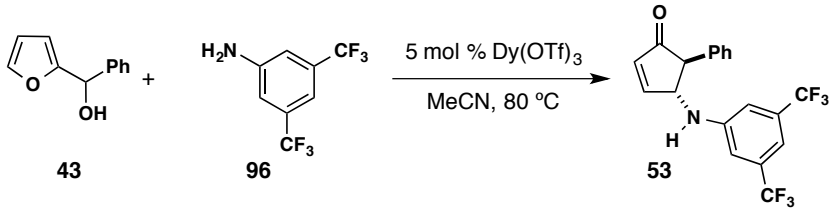
43 94 51

4-((4-methoxyphenyl)amino)-5-phenylcyclopent-2-enone (51): According to the general procedure $Dy(OTf)_3$ (69 mg, 0.114 mmol, 0.2 equiv) was added to furan-2-yl(phenyl)methanol **43** (100 mg, 0.57 mmol, 1 equiv) and 4-methoxyaniline **94** (78 mg, 0.57 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **51** (99 mg, 62%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.7, 2.3 Hz, 1H), 7.38 – 7.24 (m, 3H), 7.12 (d, J = 7.2 Hz, 2H), 6.72 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 6.39 (dd, J = 5.7, 1.5 Hz, 1H), 4.67 (d, J = 1.7 Hz, 1H), 3.73 (s, 3H), 3.38 (d, J = 2.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 162.3, 153.2, 140.2, 138.3, 134.8, 129.1, 128.2, 127.5, 115.8, 115.1, 64.6, 60.1, 55.8 ppm; IR (thin film) 3363, 3031, 2935, 2835, 1709, 1593, 1512, 1242 cm^{-1}; HRMS (ESI) *m/z* 302.1154 (302.1151 calcd for $C_{18}H_{17}NO_2Na^+$ $[M + Na]^+$).



43 95 52

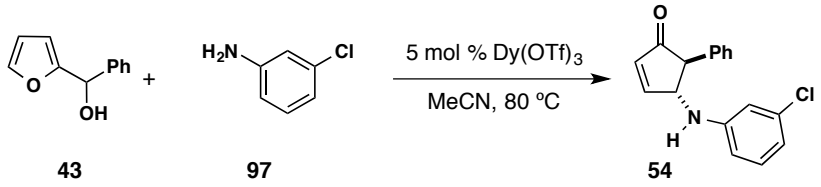
4-((3,5-dimethylphenyl)amino)-5-phenylcyclopent-2-enone (52): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (100 mg, 0.58 mmol, 1 equiv) and 3,5-dimethylaniline **95** (70 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **52** (130 mg, 81%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, J = 5.7, 2.2 Hz, 1H), 7.43 – 7.29 (m, 3H), 7.17 (d, J = 7.2 Hz, 2H), 6.47 – 6.39 (m, 2H), 6.16 (s, 2H), 4.75 (d, J = 1.6 Hz, 1H), 3.94 (bs, 1H), 3.40 (d, J = 2.5 Hz, 1H), 2.17 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.9, 162.1, 146.3, 139.3, 138.5, 134.8, 129.1, 128.3, 127.5, 120.8, 112.1, 63.7, 60.5, 21.6 ppm; IR (thin film) 3375, 3028, 2916, 2858, 1709, 1600, 1492, 1338 cm^{-1}; HRMS (ESI) *m/z* 300.1359 (300.1359 calcd for $C_{19}H_{19}NONa^+$ $[M + Na]^+$).



43 96 53

4-((3,5-bis(trifluoromethyl)phenyl)amino)-5-phenylcyclopent-2-enone (53): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to

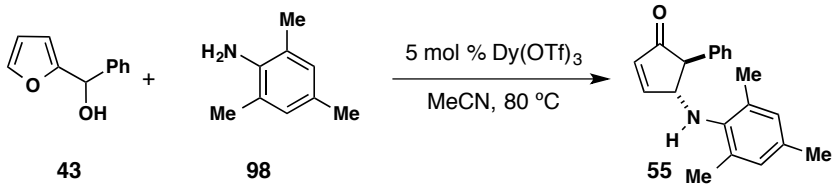
furan-2-yl(phenyl)methanol **43** (103 mg, 0.592 mmol, 1 equiv) and 3,5-bis(trifluoromethyl)aniline **96** (97 mg, 0.8 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **53** (171 mg, 75%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 5.7, 2.4 Hz, 1H), 7.40 – 7.28 (m, 3H), 7.17 (s, 1H), 7.14 – 7.08 (m, 2H), 6.80 (s, 2H), 6.49 (dd, *J* = 5.7, 1.8 Hz, 1H), 4.78 (dddd, *J* = 8.2, 2.3, 2.3, 2.3 Hz, 1H), 4.60 (d, *J* = 8.2 Hz, 1H), 3.34 (d, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 160.2, 147.1, 137.6, 135.9, 132.8 (q, *J* = 32.9 Hz), 129.5, 128.1, 128.0, 123.4 (q, *J* = 272.8 Hz), 113.1 (d, *J* = 2.9 Hz), 111.7 (dddd, *J* = 3.8, 3.8, 3.8, 3.8 Hz), 63.3, 60.8 ppm; IR (thin film) 3375, 3055, 2908, 1705, 1600, 1315 cm^{-1}; HRMS (ESI) *m/z* 408.0799 (408.0794 calcd for $C_{19}H_{13}F_6NONa^+$ [M + Na]$^+$).



43 97 54

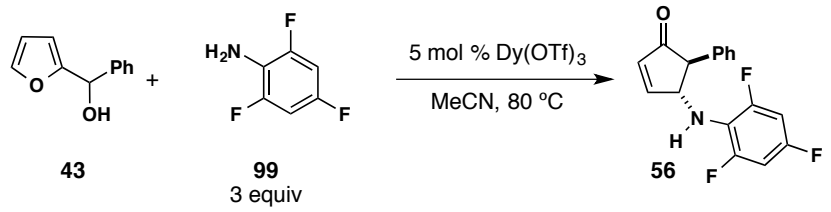
4-((3-chlorophenyl)amino)-5-phenylcyclopent-2-enone (54): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (100 mg, 0.58 mmol, 1 equiv) and 3-chloroaniline **97** (73 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 20 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified

by column chromatography to afford cyclopentenone **54** (134 mg, 82%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.16 – 7.12 (m, 2H), 7.03 (t, *J* = 8.1 Hz, 1H), 6.74 – 6.69 (m, 1H), 6.49 (t, *J* = 2.1 Hz, 1H), 6.44 (dd, *J* = 5.7, 1.7 Hz, 1H), 6.38 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.72 (dddd, *J* = 8.3, 2.1, 2.1, 2.1 Hz, 1H), 4.16 (d, *J* = 8.5 Hz, 1H), 3.38 (d, *J* = 2.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 161.3, 147.5, 137.9, 135.3, 135.2, 130.6, 129.3, 128.1, 127.7, 118.7, 113.8, 112.1, 63.3, 60.3 ppm; IR (thin film) 3376, 3062, 3029, 1704, 1596, 1327 cm^{-1}; HRMS (ESI) *m/z* 306.0656 (306.0656 calcd for $C_{17}H_{14}ClNONa^{+}$ $[M + Na]^{+}$).



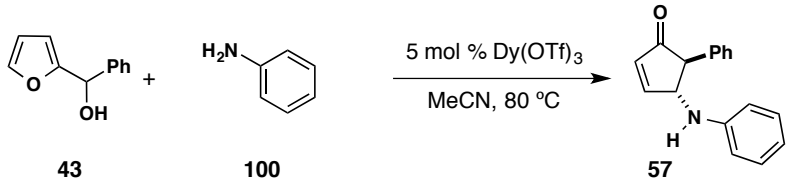
4-(mesitylamino)-5-phenylcyclopent-2-enone (55): According to the general procedure $Dy(OTf)_3$ (20 mg, 0.033 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (114 mg, 0.66 mmol, 1 equiv) and 2,4,6-trimethylaniline **98** (92µl, 0.66 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **55** (175 mg, 91%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.33 – 7.21 (m, 3H), 7.06 – 7.00 (m, 2H), 6.81 (bs, 2H), 6.34 (dd, *J* = 5.7, 1.4 Hz, 1H), 4.43 (s, 1H), 3.40 (d, *J* = 2.9 Hz, 1H), 3.17 (bs, 1H), 2.23 (s, 3H), 2.10 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 163.1, 140.9, 138.1, 133.7, 132.5, 130.0, 129.9,

128.9, 128.1, 127.3, 67.7, 60.6, 20.8, 18.8 ppm; IR (thin film) 3359, 2920, 1708, 1589, 1485, 1230 cm^{-1}; HRMS (ESI) *m/z* 314.1512 (314.1515 calcd for $C_{20}H_{21}NONa^+$ $[M + Na]^+$).



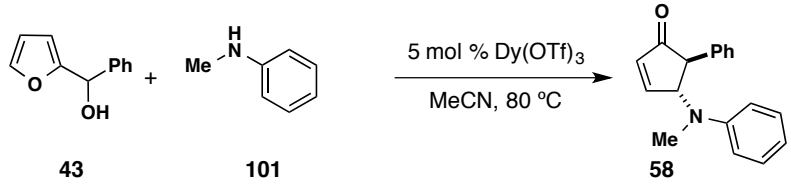
43 99 3 equiv 56

5-phenyl-4-((2,4,6-trifluorophenyl)amino)cyclopent-2-enone (50): According to the general procedure $Dy(OTf)_3$ (21 mg, 0.035 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (120 mg, 0.69 mmol, 1 equiv) and 2,4,6-trifluoroaniline **99** (304 mg, 2.1 mmol, 3 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to proceed at rt for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **56** (155 mg, 74%) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.8, 2.2 Hz, 1H), 7.32 – 7.20 (m, 3H), 7.04 – 6.93 (m, 2H), 6.64 – 6.56 (m, 2H), 6.37 (dd, *J* = 5.8, 1.7 Hz, 1H), 4.85 – 4.74 (m, 1H), 3.56 (d, *J* = 10.0 Hz, 1H), 3.34 (d, *J* = 3.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.0, 161.7, 156.3 (ddd, *J* = 243.9, 15.0, 15.0 Hz), 154.5 (ddd, *J* = 244.1, 14.5, 9.0 Hz), 137.3, 134.6, 128.9, 128.0, 127.4, 120.4 (ddd, *J* = 15.1, 15.1, 4.7 Hz), 100.6 (dddd, *J* = 26.2, 26.2, 20.5, 8.6 Hz), 66.1 (dd, *J* = 2.9, 2.9 Hz), 61.2 ppm; IR (thin film) 3344, 3070, 1712, 1612, 1508, 1442 cm^{-1}; HRMS (ESI) *m/z* 326.0782 (326.0763 calcd for $C_{17}H_{12}F_3NONa^+$ $[M + Na]^+$).



43 100 57

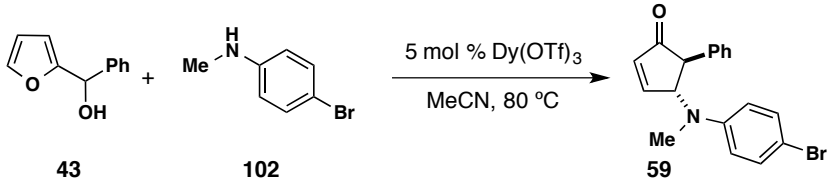
5-phenyl-4-(phenylamino)cyclopent-2-enone (57): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (100 mg, 0.58 mmol, 1 equiv) and aniline **100** (54 mg, 0.58 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **57** (124 mg, 86%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J = 5.7, 2.3 Hz, 1H), 7.41 – 7.30 (m, 3H), 7.20 – 7.12 (m, 4H), 6.78 (dd, J = 10.6, 4.1 Hz, 1H), 6.57 – 6.51 (m, 2H), 6.41 (dd, J = 5.7, 1.6 Hz, 1H), 4.76 (bs, 1H), 4.11 (bs, 1H), 3.41 (d, J = 2.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 162.0, 146.3, 138.1, 134.7, 129.5, 129.1, 128.1, 127.5, 118.7, 113.9, 63.4, 60.1 ppm; IR (thin film) 3374, 3053, 3027, 1708, 1601, 1497, 1314 cm^{-1}; HRMS (ESI) *m/z* 272.1049 (272.1046 calcd for $C_{17}H_{15}NONa^+$ [M + Na]$^+$).



43 101 58

4-(methyl(phenyl)amino)-5-phenylcyclopent-2-enone (58): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.029 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (100 mg, 0.57 mmol, 1 equiv) and 2,6-dimethyl aniline **101** (61 mg,

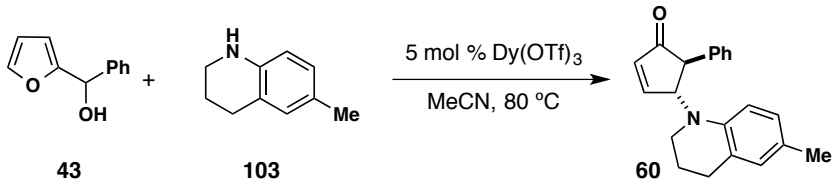
0.57 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **58** (111 mg, 74%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.35 – 7.24 (m, 3H), 7.13 (t, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 6.48 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.16 – 5.12 (m, 1H), 3.53 (d, *J* = 2.9 Hz, 1H), 2.86 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 163.5, 149.4, 138.5, 135.3, 129.4, 129.2, 128.3, 127.4, 118.6, 114.6, 70.1, 56.3, 33.5 ppm; IR (thin film) 3059, 2916, 2812, 1709, 1597, 1500, 1377 cm^{-1}; HRMS (ESI) *m/z* 286.1199 (286.1202 calcd for $C_{18}H_{17}NONa^+[M + Na]^+$).



43 102 59

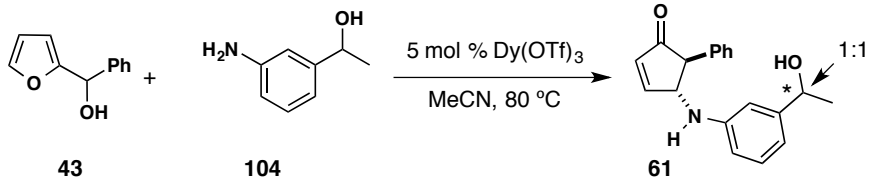
4-((4-bromophenyl)(methyl)amino)-5-phenylcyclopent-2-enone (59): According to the general procedure $Dy(OTf)_3$ (21 mg, 0.034 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (119 mg, 0.68 mmol, 1 equiv) and 4-bromo-N-methylaniline **102** (127 mg, 0.68 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 45 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **59** (205 mg, 88%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.37 – 7.24 (m, 3H), 7.24 –

7.15 (m, 2H), 7.10 – 7.04 (m, 2H), 6.51 – 6.43 (m, 3H), 5.13 – 5.04 (m, 1H), 3.48 (d, J = 3.0 Hz, 1H), 2.82 (s, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.3, 162.8, 148.4, 138.2, 135.5, 132.0, 129.3, 128.3, 127.5, 115.9, 110.4, 69.8, 56.4, 33.3 ppm; IR (thin film) 3062, 2896, 2815, 1712, 1589, 1496, 1311 cm^{-1}; HRMS (ESI) *m/z* 364.0306 (364.0307 calcd for $C_{18}H_{16}BrNONa^+$ $[M + Na]^+$).



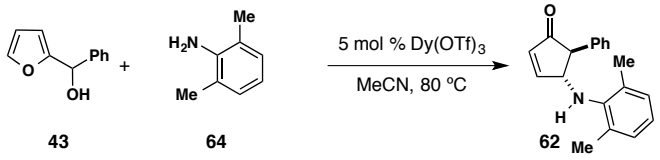
43 103 60

4-(6-methyl-3,4-dihydroquinolin-1(2H)-yl)-5-phenylcyclopent-2-enone (60): According to the general procedure $Dy(OTf)_3$ (18 mg, 0.03 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (105 mg, 0.6 mmol, 1 equiv) and 6-methyl-1,2,3,4-tetrahydroquinoline **103** (87 mg, 0.6 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **60** (122 mg, 67%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, J = 5.7, 2.2 Hz, 1H), 7.33 – 7.21 (m, 3H), 7.06 – 7.00 (m, 2H), 6.81 (s, 2H), 6.34 (dd, J = 5.7, 1.4 Hz, 1H), 4.43 (s, 1H), 3.40 (d, J = 2.9 Hz, 1H), 3.17 (bs, 1H), 2.23 (s, 3H), 2.10 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 164.2, 142.4, 138.8, 135.1, 130.3, 129.2, 128.2, 127.5, 127.3, 126.6, 123.9, 112.5, 68.7, 55.9, 44.5, 28.1, 22.9, 20.3 ppm; IR (thin film) 3020, 2931, 2854, 1709, 1504, 1296 cm^{-1}; HRMS (ESI) *m/z* 326.1524 (326.1515 calcd for $C_{21}H_{21}NONa^+$ $[M + Na]^+$).



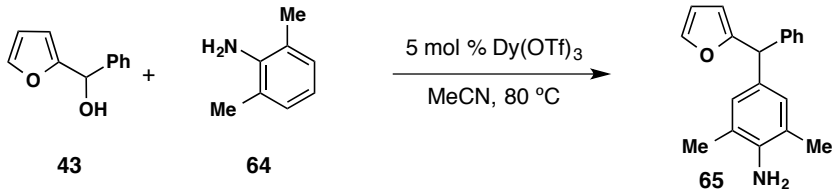
43 **104** **61**

4-((4-(1-hydroxyethyl)phenyl)amino)-5-phenylcyclopent-2-enone (61): According to the general procedure $Dy(OTf)_3$ (23 mg, 0.038 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (130 mg, 0.75 mmol, 1 equiv) and 1-(4-aminophenyl)ethanol **104** (103 mg, 0.75 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **61** (193 mg, 88%) as an oil. ^{1}H NMR of 1:1 mixture of diastereomers (500 MHz, $CDCl_3$) δ 7.75 (dd, J = 5.7, 2.3 Hz, 1H), 7.39 – 7.28 (m, 3H), 7.17 – 7.06 (m, 3H), 6.71 (dd, J = 7.4, 3.5 Hz, 1H), 6.50 (d, J = 9.6 Hz, 1H), 6.46 – 6.37 (m, 2H), 4.78 (s, 1H), 4.67 (dddd, J = 6.4, 6.4, 6.4, 1.9 Hz, 1H), 4.14 (bs, 1H), 3.36 (d, J = 2.5 Hz, 1H), 1.94 (bs, 1H), 1.35 (dd, J = 6.3, 5.3 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.8, 206.8, 162.0, 161.9, 147.5, 147.5, 146.5, 146.5, 138.3, 138.3, 134.8, 134.8, 129.6, 129.62, 129.1, 129.1, 128.2, 128.2, 127.5, 115.9, 115.8, 113.1, 113.0, 110.9, 110.8, 70.3, 63.5, 63.4, 60.6, 60.5, 25.1, 25.0 ppm; IR (thin film) 3375, 3032, 2970, 2920, 1705, 1601, 1489, 1331 cm^{-1}; HRMS (ESI) *m/z* 316.1309 (316.1308 calcd for $C_{19}H_{19}NO_2Na^+$[M + Na]$^+$).



43 **64** **62**

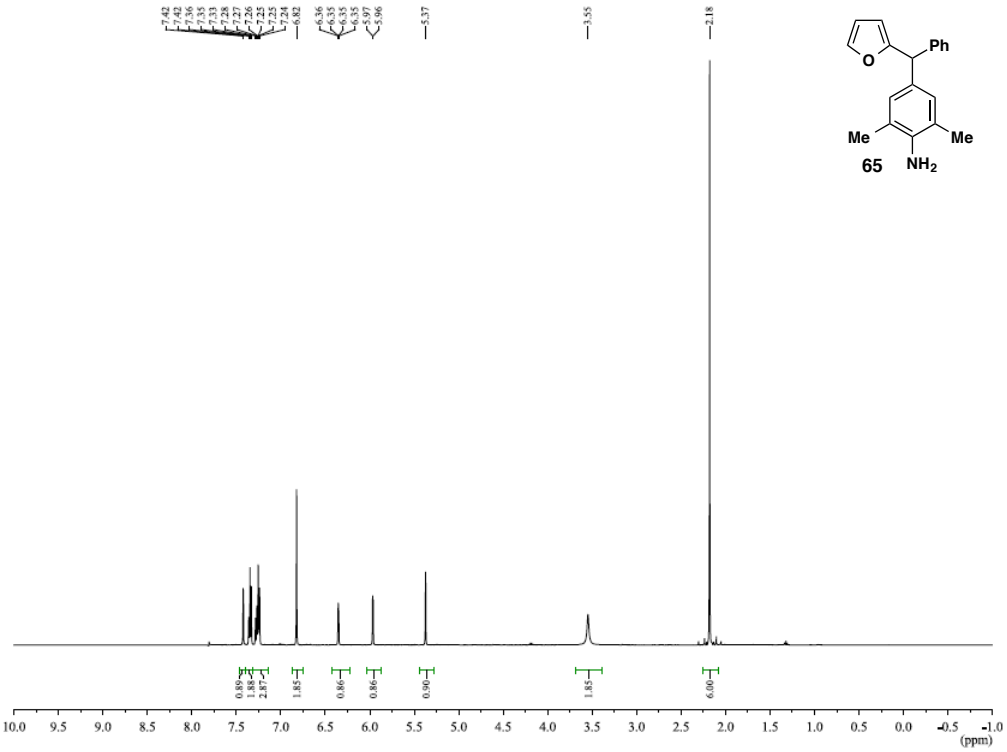
4-((2,6-dimethylphenyl)amino)-5-phenylcyclopent-2-enone (62): According to the general procedure $Dy(OTf)_3$ (20 mg, 0.03 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **43** (115 mg, 0.66 mmol, 1 equiv) and 2,6-dimethylaniline **64** (82 µl, 0.66 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **62** (60 mg, 33%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.31 – 7.22 (m, 4H), 7.02 – 6.95 (m, 4H), 6.90 – 6.83 (m, 1H), 6.36 (dd, *J* = 5.7, 1.6 Hz, 1H), 4.50 – 4.47 (m, 1H), 3.39 (d, *J* = 2.9 Hz, 1H), 2.13 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 163.0, 143.6, 138.1, 134.0, 129.9, 129.3, 129.0, 128.1, 127.4, 123.2, 67.4, 60.7, 19.0 ppm; IR (thin film) 3359, 3032, 2927, 1709, 1469, 1219 cm^{-1}; HRMS (ESI) *m/z* 300.1358 (300.1359 calcd for $C_{19}H_{19}NONa^+$ [M + Na]$^+$).

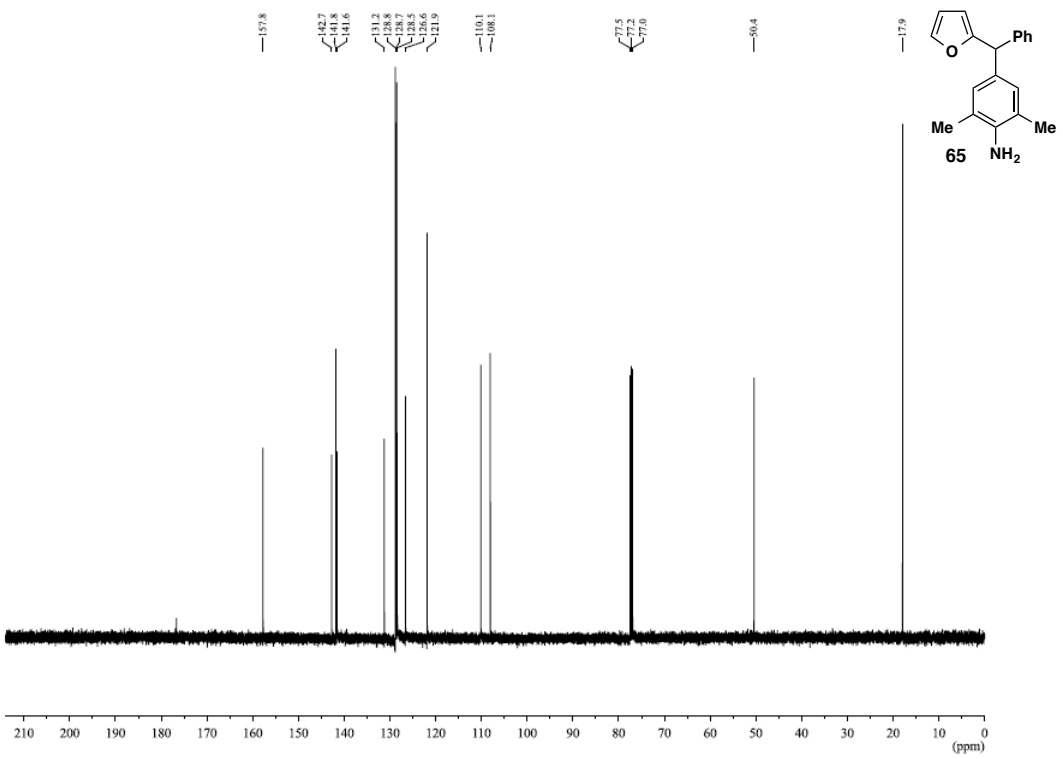


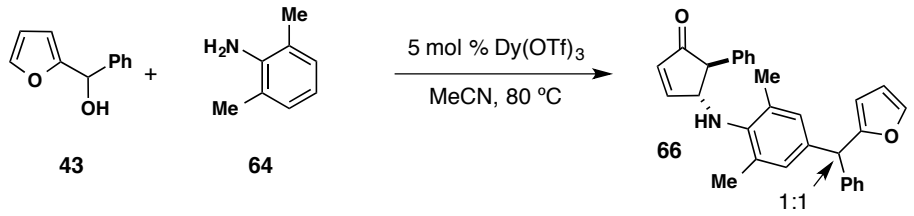
43 64 65

4-(furan-2-yl(phenyl)methyl)-2,6-dimethylaniline (65): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol **43** (100 mg, 0.71 mmol, 1 equiv) and 2,6-dimethylaniline **64** (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified

by column chromatography to afford **65** (60 mg, 38%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 1.0 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.21 (m, 3H), 6.82 (s, 2H), 6.35 (dd, *J* = 3.0, 1.9 Hz, 1H), 5.96 (d, *J* = 3.2 Hz, 1H), 5.37 (bs, 1H), 3.55 (s, 2H), 2.18 (s, 6H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.8, 142.7, 141.8, 141.6, 131.2, 128.8, 128.7, 128.5, 126.6, 121.8, 110.1, 108.0, 50.4, 17.9 ppm; IR (thin film) 3473, 3114, 3025, 1624, 1599 cm^{-1}; HRMS (ESI) *m/z* 278.1536 (278.1467 calcd for $C_{17}H_{23}NOH^{+}$ $[M + H]^{+}$).

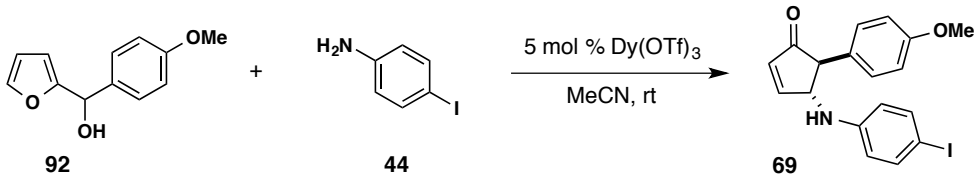






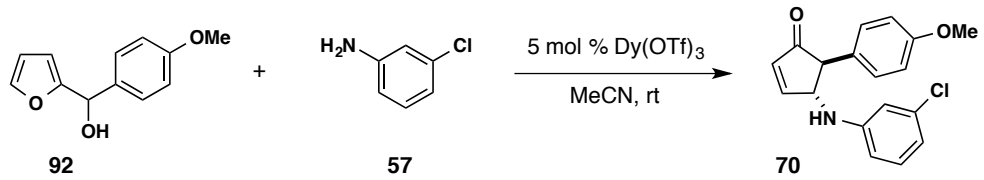
((4-(furan-2-yl(phenyl)methyl)-2,6-dimethylphenyl)amino)-5-phenylcyclopent-2-enone (66): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol **43** (100 mg, 0.71 mmol, 1 equiv) and 2,6-dimethylaniline **64** (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **66** (37 mg,

15%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.7, 1.8 Hz, 1H), 7.41 – 7.39 (m, 1H), 7.35 – 7.31 (m, 2H), 7.28 – 7.23 (m, 4H), 7.20 – 7.16 (m, 2H), 6.98 – 6.92 (m, 2H), 6.80 (s, 2H), 6.37 (dd, *J* = 5.7, 0.7 Hz, 1H), 6.34 – 6.32 (m, 1H), 5.90 (d, *J* = 2.5 Hz, 1H), 5.34 (s, 1H), 4.49 (s, 1H), 3.38 (d, *J* = 2.7 Hz, 1H), 3.26 (bs, 1H), 2.10 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.1, 163.0, 157.2, 142.3, 142.0, 138.1, 136.3, 134.0, 123.0, 129.6, 129.5, 128.9, 128.8, 128.6, 128.1, 127.3, 126.9, 110.3, 108.3, 67.4, 60.8, 50.5, 19.1 ppm; HRMS (ESI) *m/z* 456.19 (456.20 calcd for $C_{30}H_{27}NO2Na^{+}$ $[M + Na]^{+}$).

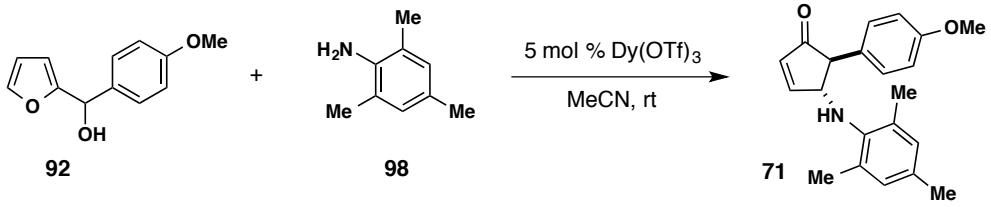


4-((4-iodophenyl)amino)-5-(4-methoxyphenyl)cyclopent-2-enone (69): According to the general procedure $Dy(OTf)_3$ (15 mg, 0.025 mmol, 0.05 equiv) was added to furan-2-yl(4-methoxyphenyl)methanol **92** (100 mg, 0.49 mmol, 1 equiv) and 4-iodoaniline **44** (107 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 1.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **69** (135 mg, 68%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 5.7, 2.2 Hz, 1H), 7.37 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.41 (dd, *J* = 5.7, 1.5 Hz, 1H), 6.29 (d, *J* = 8.7 Hz, 2H), 4.66 (s, 1H), 4.10 (bs, 1H), 3.81 (s, 3H), 3.30 (d, *J* = 2.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.7, 161.2, 159.1, 146.0, 138.1, 135.2, 130.0, 129.1, 116.1, 114.7, 79.7, 63.3,

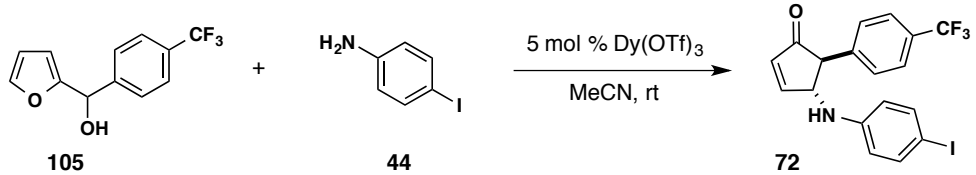
59.5, 55.5 ppm; IR (thin film) 3374, 2931, 2839, 1709, 1589, 1504, 1300 cm^{-1}; HRMS (ESI) *m/z* 428.0118 (428.0118 calcd for $C_{18}H_{16}INO_2Na^+$ $[M + Na]^+$).



4-((3-chlorophenyl)amino)-5-(4-methoxyphenyl)cyclopent-2-enone (70): According to the general procedure $Dy(OTf)_3$ (15 mg, 0.025 mmol, 0.05 equiv) was added to furan-2-yl(4-methoxyphenyl)methanol **92** (100 mg, 0.49 mmol, 1 equiv) and 3-chloroaniline **57** (63 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 6.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **70** (126 mg, 82%) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.09 – 7.00 (m, 3H), 6.92 – 6.87 (m, 2H), 6.73 – 6.69 (m, 1H), 6.51 (t, *J* = 2.0 Hz, 1H), 6.44 (dd, *J* = 5.8, 1.6 Hz, 1H), 6.40 (dd, *J* = 8.2, 1.8 Hz, 1H), 4.68 (dd, *J* = 8.4, 1.8 Hz, 1H), 4.06 (bs, 1H), 3.81 (s, 3H), 3.34 (d, *J* = 2.7 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 161.1, 159.2, 147.5, 135.4, 135.3, 130.6, 129.9, 129.2, 118.8, 114.8, 113.9, 112.1, 63.5, 59.6, 55.5 ppm; IR (thin film) 3371, 2927, 1708, 1597, 1512, 1250 cm^{-1}; HRMS (ESI) *m/z* 336.0757 (336.0762 calcd for $C_{18}H_{16}ClNO_2Na^+$ $[M + Na]^+$).

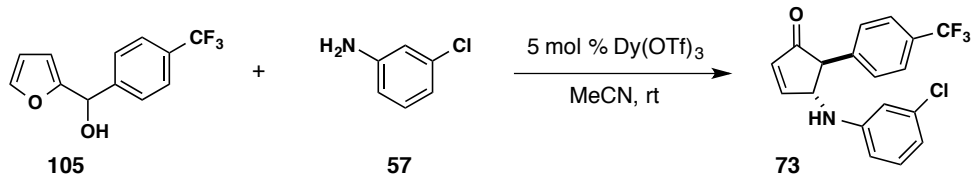


4-(mesitylamino)-5-(4-methoxyphenyl)cyclopent-2-enone (71): According to the general procedure $Dy(OTf)_3$ (30 mg, 0.05 mmol, 0.1 equiv) was added to furan-2-yl(4-methoxyphenyl)methanol **92** (100 mg, 0.49 mmol, 1 equiv) and 2,4,6-trimethylaniline **98** (66 mg, 0.49 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was allowed to react at rt for 5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **71** (140 mg, 89%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (ddd, J = 5.7, 2.0, 2.0 Hz, 1H), 6.98 – 6.92 (m, 2H), 6.89 – 6.79 (m, 4H), 6.33 (ddd, J = 5.7, 1.5, 1.5 Hz, 1H), 4.39 (s, 1H), 3.80 (d, J = 1.8 Hz, 3H), 3.35 (d, J = 2.8 Hz, 1H), 3.16 (s, 1H), 2.24 (s, 3H), 2.12 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5, 163.0, 158.8, 141.0, 133.7, 132.5, 130.1, 130.0, 129.9, 129.2, 114.4, 67.7, 59.9, 55.4, 20.8, 18.9 ppm; IR (thin film) 3357, 2996, 2915, 2835, 1713, 1612, 1513, 1250 cm^{-1}; HRMS (ESI) *m/z* 344.1618 (344.1621 calcd for $C_{21}H_{23}NO_2Na^+$ $[M + Na]^+$).



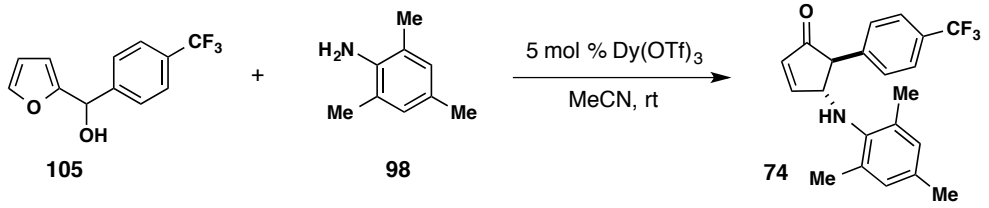
4-((4-iodophenyl)amino)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-enone (72): According to the general procedure $Dy(OTf)_3$ (13 mg, 0.020 mmol, 0.05 equiv) was added to

furan-2-yl(4-(trifluoromethyl)phenyl)methanol **105** (100 mg, 0.41 mmol, 1 equiv) and 4-iodoaniline **44** (90 mg, 0.41 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 4.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **72** (151 mg, 83%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.43 – 7.35 (m, 2H), 7.29 – 7.23 (m, 2H), 6.46 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.33 – 6.25 (m, 2H), 4.73 (bs, 1H), 4.08 (bs, 1H), 3.44 (d, *J* = 2.6 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.2, 161.4, 145.6, 141.9, 138.3, 135.2, 130.0 (q, *J* = 32.6 Hz), 128.5, 126.2 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272.2 Hz), 116.1, 80.2, 63.0, 59.9 ppm; IR (thin film) 3379, 3062, 2924, 1712, 1589, 1496, 1327 cm^{-1}; HRMS (ESI) *m/z* 444.0062 (444.0067 calcd for $C_{18}H_{13}F_3INOH^+$ $[M + H]^+$).



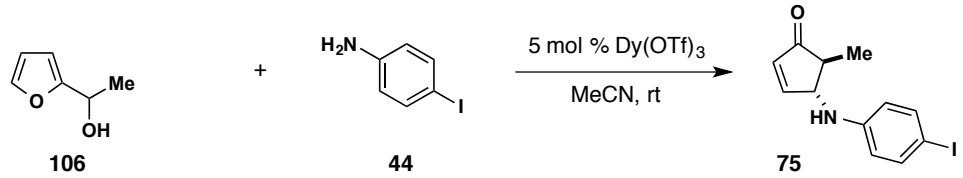
4-((3-chlorophenyl)amino)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-enone (73): According to the general procedure $Dy(OTf)_3$ (14 mg, 0.024 mmol, 0.05 equiv) was added to furan-2-yl(4-(trifluoromethyl)phenyl)methanol **105** (115 mg, 0.47 mmol, 1 equiv) and 3-chloroaniline **57** (61 mg, 0.47 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue

was purified by column chromatography to afford cyclopentenone **73** (144 mg, 87%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.05 (t, *J* = 8.1 Hz, 1H), 6.74 (ddd, *J* = 7.9, 1.9, 0.8 Hz, 1H), 6.50 – 6.46 (m, 2H), 6.38 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H), 4.75 (bs, 1H), 4.08 (bs, 1H), 3.47 (d, *J* = 2.8 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.1, 161.3, 147.1, 141.9, 135.5, 135.3, 130.7, 130.1 (d, *J* = 32.7 Hz), 128.6, 126.3 (q, *J* = 3.8 Hz), 119.2, 112.2, 63.2, 60.1 ppm; IR (thin film) 3375, 3070, 2924, 1712, 1597, 1508, 1327 cm^{-1}; HRMS (ESI) *m/z* 374.0538 (374.0530 calcd for $C_{18}H_{13}ClF_3NONa^+$ $[M + Na]^+$).

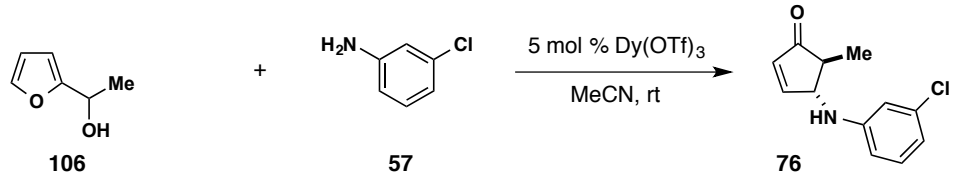


4-(mesitylamino)-5-(4-(trifluoromethyl)phenyl)cyclopent-2-enone (74): According to the general procedure $Dy(OTf)_3$ (25 mg, 0.041 mmol, 0.1 equiv) was added to furan-2-yl(4-(trifluoromethyl)phenyl)methanol **105** (100 mg, 0.41 mmol, 1 equiv) and 2,4,6-trimethylaniline **98** (56 mg, 0.41 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 8 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **74** (115 mg, 78%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 5.6, 1.4 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.82 (s, 2H), 6.37 (d, *J* = 5.6 Hz, 1H), 4.44 (bs, 1H), 3.46 (d, *J* = 2.6 Hz, 1H), 3.20 (bs, 1H), 2.24 (s, 3H), 2.11 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ δ

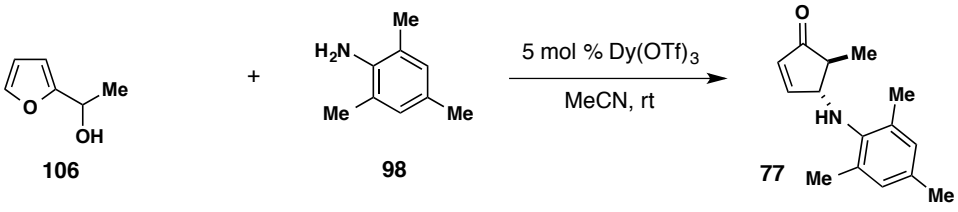
206.0, 163.1, 142.1, 140.6, 133.7, 132.9, 129.9, 129.6 (q, J = 32.5 Hz), 128.6, 125.9 (q, J = 3.7 Hz), 124.3 (q, J = 272.0 Hz), 67.4, 60.4, 20.8, 18.8 ppm; IR (thin film) 3359, 2924, 2858, 1712, 1616, 1481, 1326 cm^{-1}; HRMS (ESI) *m/z* 382.1405 (382.1389 calcd for $C_{21}H_{20}F_3NONa^+$ $[M + Na]^+$).



4-((4-iodophenyl)amino)-5-methylcyclopent-2-enone (75): According to the general procedure $Dy(OTf)_3$ (27 mg, 0.045 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol **106** (100 mg, 0.89 mmol, 1 equiv) and 4-iodoaniline **44** (195 mg, 0.89 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 2.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **75** (190 mg, 68%) as an oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.59 (dd, J = 5.8, 2.2 Hz, 1H), 7.49 – 7.46 (m, 2H), 6.50 – 6.47 (m, 2H), 6.28 (dd, J = 5.8, 1.6 Hz, 1H), 4.34 – 4.29 (m, 1H), 3.83 (d, J = 8.8 Hz, 1H), 2.22 (dddd, J = 7.4, 7.4, 7.4, 2.9 Hz, 1H), 1.33 (d, J = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 160.4, 146.4, 138.3, 134.4, 115.9, 79.6, 61.9, 49.1, 14.6 ppm; IR (thin film) 3367, 3062, 2970, 1709, 1589, 1496, 1315 cm^{-1}; HRMS (ESI) *m/z* 335.9860 (335.9856 calcd for $C_{12}H_{12}INONa^+$ $[M + Na]^+$).

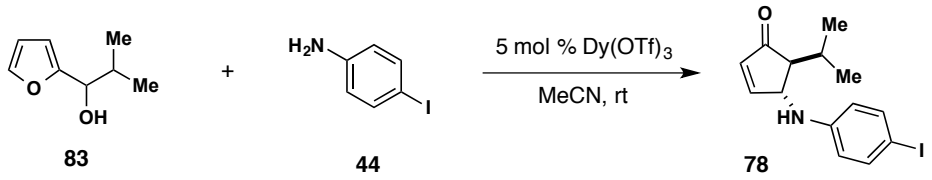


4-((3-chlorophenyl)amino)-5-methylcyclopent-2-enone (76): According to the general procedure $Dy(OTf)_3$ (60 mg, 0.1 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol **106** (222 mg, 1.98 mmol, 1 equiv) and 3-chloroaniline **57** (253 mg, 1.98 mmol, 1 equiv) in 15 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 3 h. The reaction was then quenched with 10 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **76** (44 mg, 10%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 5.7, 1.9 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.60 – 6.52 (m, 1H), 6.29 (d, *J* = 5.7 Hz, 1H), 4.33 (d, *J* = 8.0 Hz, 1H), 3.86 (d, *J* = 8.8 Hz, 1H), 2.23 (dddd, *J* = 7.4, 7.4, 7.4, 2.8 Hz, 1H), 1.35 (d, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7, 160.4, 147.9, 135.5, 134.4, 130.8, 118.7, 113.4, 112.0, 61.9, 49.1, 14.6 ppm; IR (thin film) 3367, 2968, 2930, 1709, 1598, 1483, 1324 cm^{-1}. HRMS (ESI) *m/z* 244.0505 (244.0505 calcd for $C_{14}H_{12}ClNONa^+$ $[M + Na]^+$).



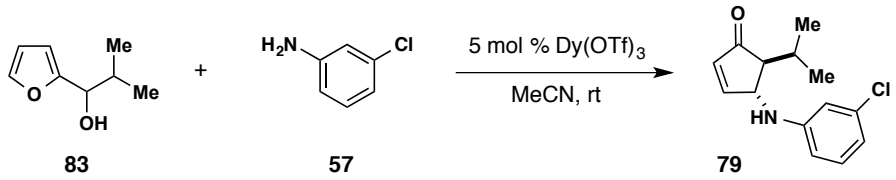
4-(mesitylamino)-5-methylcyclopent-2-enone (77): According to the general procedure $Dy(OTf)_3$ (27 mg, 0.45 mmol, 0.05 equiv) was added to 1-(furan-2-yl)ethanol **105** (100 mg, 0.89 mmol, 1 equiv) and 2,4,6-trimethylaniline **98** (125 µl, 0.89 mmol, 1 equiv) in 6 mL of

MeCN. The resulting reaction mixture was heated to 80 ºC for 3.5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **77** (151 mg, 74%) as a solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 5.7, 1.9 Hz, 1H), 6.88 (s, 2H), 6.19 (d, *J* = 5.7 Hz, 1H), 4.00 – 3.98 (m, 1H), 2.98 (bs, 1H), 2.29 (s, 6H), 2.26 (s, 3H), 2.24 (dddd, *J* = 7.4, 7.4, 7.4, 2.9 Hz, 1H), 1.26 (d, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (125 MHz, CDC_3) δ 209.3, 162.5, 141.2, 133.1, 132.4, 129.9, 129.9, 66.3, 49.6, 20.8, 18.8, 13.9 ppm; IR (thin film) 3356, 2927, 1712, 1481, 1234 cm^{-1}; HRMS (ESI) *m/z* 252.1364 (252.1359 calcd for $C_{15}H_{19}NONa^+$ $[M + Na]^+$).



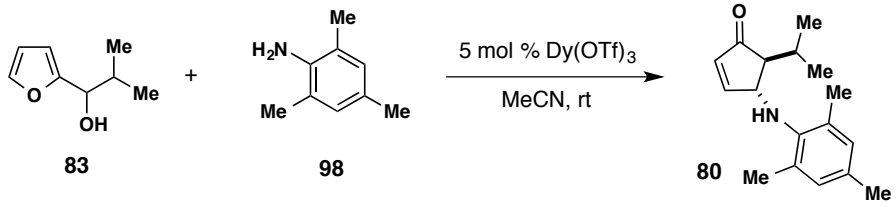
4-((4-iodophenyl)amino)-5-isopropylcyclopent-2-enone (78): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol **83** (100 mg, 0.71 mmol, 1 equiv) and 4-iodoaniline **44** (156 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 5 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **78** (176 mg, 73%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 5.7, 2.1 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.27 (s, 1H), 6.54 – 6.42 (m, 2H), 6.20 (dd, *J* = 5.8, 1.4 Hz, 1H), 4.48 (d, *J* = 8.8 Hz, 1H), 3.84 (d, *J* = 8.6 Hz, 1H), 2.43 –

2.25 (m, 1H), 2.16 (dd, *J* = 4.1, 3.1 Hz, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.3, 161.3, 146.2, 138.3, 134.9, 115.8, 79.3, 59.1, 56.4, 28.1, 20.6, 18.6 ppm; IR (thin film) 3371, 3062, 2958, 2877, 1589, 1496, 1319 cm^{-1}; HRMS (ESI) *m/z* 364.0168 (364.0169 calcd for $C_{14}H_{16}INONa^+$ $[M + Na]^+$).

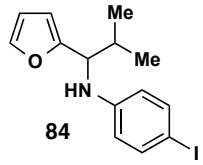


83 **57** **79**

4-((3-chlorophenyl)amino)-5-isopropylcyclopent-2-enone (79): According to the general procedure $Dy(OTf)_3$ (22 mg,0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol **83** (100 mg, 0.71 mmol, 1 equiv) and 3-chloroaniline **57** (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 6 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **79** (92 mg, 52%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 5.8, 2.1 Hz, 1H), 7.13 (dd, *J* = 8.0 Hz, 1H), 6.79 – 6.73 (m, 1H), 6.69 (dd, *J* = 2.0 Hz, 1H), 6.56 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.24 (dd, *J* = 5.7, 1.3 Hz, 1H), 4.51 (d, *J* = 7.1 Hz, 1H), 3.77 (d, *J* = 7.8 Hz, 1H), 2.41 – 2.31 (m, 1H), 2.20 – 2.14 (m, 1H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.2, 161.2, 147.7, 135.6, 135.1, 130.8, 118.6, 113.3, 112.0, 59.2, 56.4, 28.2, 20.7, 18.6 ppm; IR (thin film) 3377, 2958, 2926, 1703, 1598, 1483, 1323 cm^{-1}. HRMS (ESI) *m/z* 272.0824 (272.0818 calcd for $C_{14}H_{16}ClNONa^+$ $[M + Na]^+$).

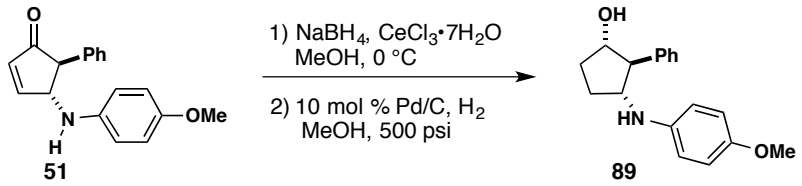


5-isopropyl-4-(mesitylamino)cyclopent-2-enone (80): According to the general procedure $Dy(OTf)_3$ (22 mg, 0.036 mmol, 0.05 equiv) was added to 1-(furan-2-yl)-2-methylpropan-1-ol **83** (100 mg, 0.71 mmol, 1 equiv) and 2,4,6-trimethylaniline **98** (91 mg, 0.71 mmol, 1 equiv) in 6 mL of MeCN. The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **80** (163 mg, 89%) as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 5.7, 2.2 Hz, 1H), 6.86 (s, 2H), 6.16 (dd, *J* = 5.7, 1.1 Hz, 1H), 4.21 (d, *J* = 1.0 Hz, 1H), 2.91 (bs, 1H), 2.35 – 2.23 (m, 11H), 2.17 (dd, *J* = 3.6, 2.6 Hz, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 163.8, 141.2, 134.17, 132.3, 130.0, 129.9, 60.4, 59.9, 28.4, 20.8, 20.5, 19.1, 18.6 ppm; IR (thin film) 3352, 2958, 1704, 1589, 1481, 1230 cm^{-1}; HRMS (ESI) *m/z* 258.1863 (258.1852 calcd for $C_{17}H_{23}NOH^+$ $[M + H]^+$).



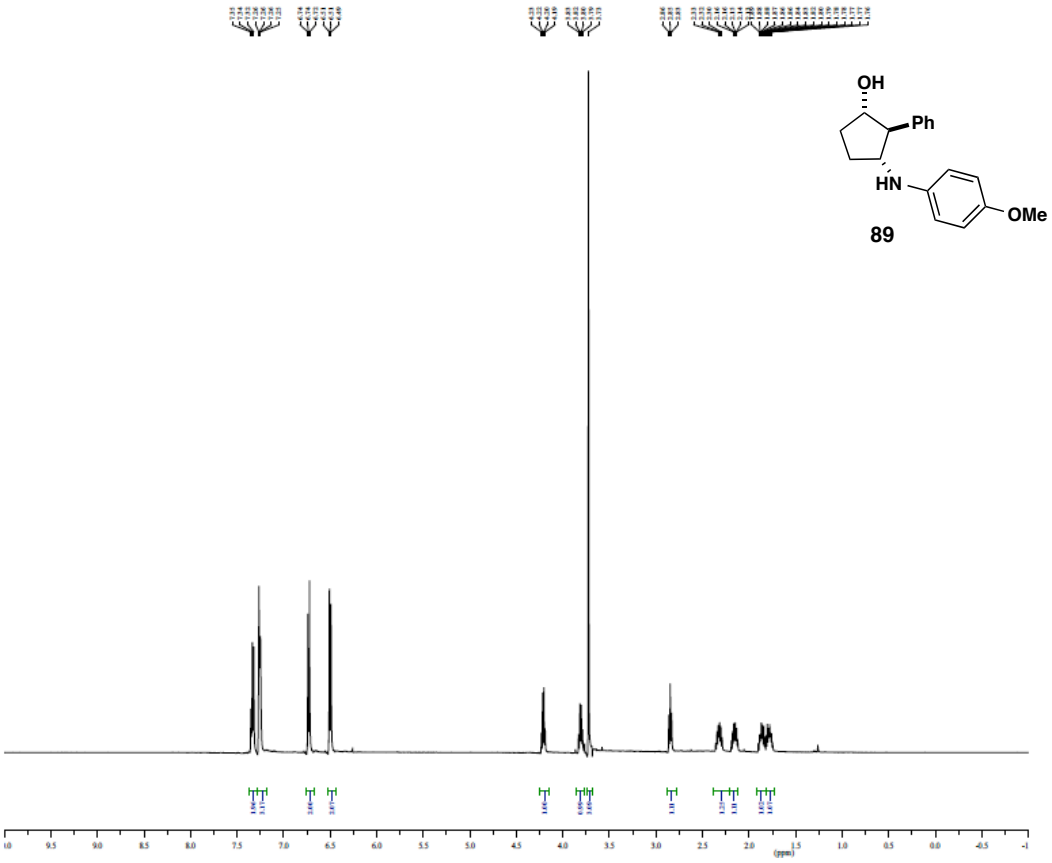
***N*-(1-(furan-2-yl)-2-methylpropyl)-4-iodoaniline (84): ^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 3.4, 1.9 Hz, 1H), 7.36 (dd, *J* = 3.0, 2.0 Hz, 1H), 7.33 – 7.31 (m, 1H), 6.38 (dd, *J* = 2.8, 1.9 Hz, 1H), 6.37 (dd, *J* = 2.8, 2.0 Hz, 1H), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.11 (d, *J* = 3.2 Hz, 1H), 4.18 (d, *J* = 6.0 Hz, 1H), 4.00 (s, 1H), 2.15 (dqq, *J* = 13.7, 6.9, 6.5 Hz, 1H),

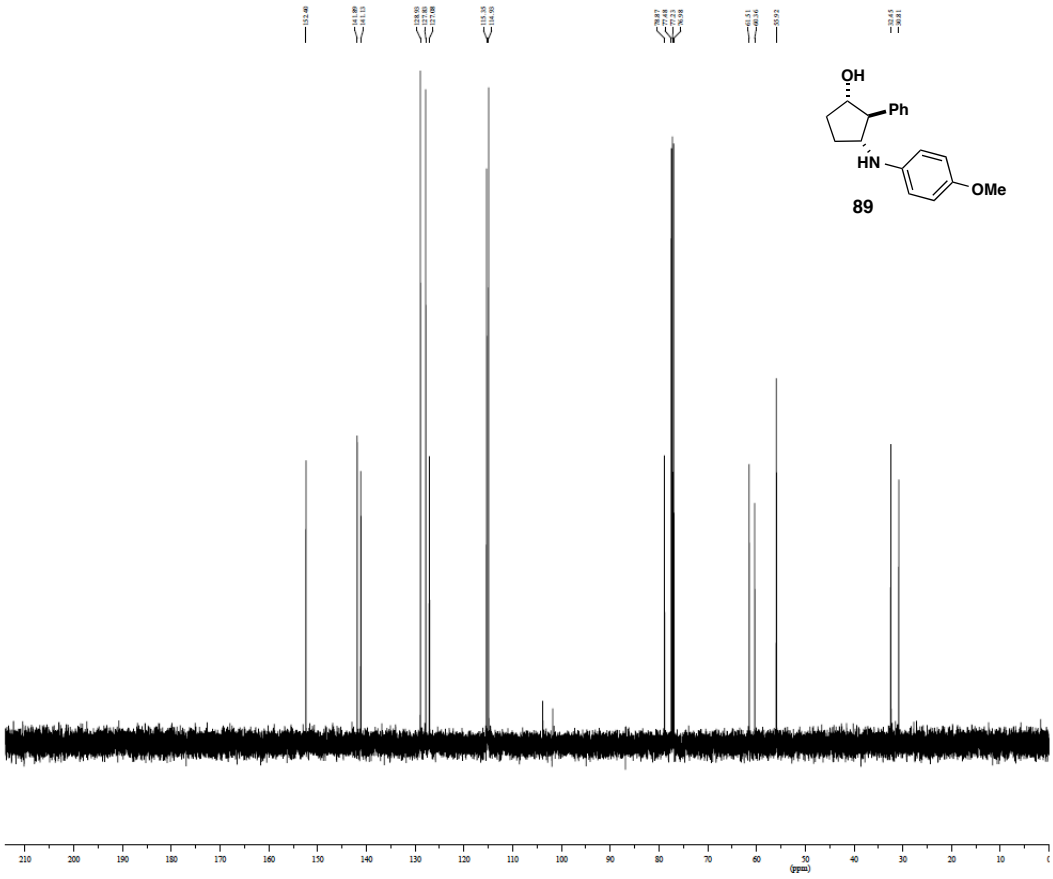
1.00 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.9, 147.2, 141.6, 137.8, 115.7, 110.2, 106.9, 78.3, 57.8, 32.9, 19.2, 19.1 ppm.

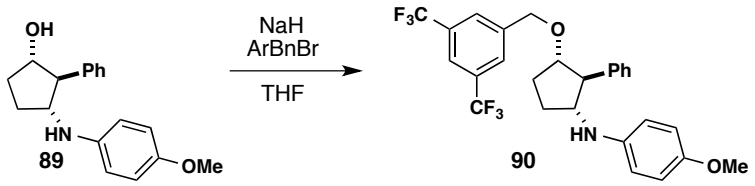


3-((4-methoxyphenyl)amino)-2-phenylcyclopentanol (89): 4-((4-methoxyphenyl)amino)-5-phenylcyclopent-2-enone **51** (399 mg, 1.43 mmol, 1 equiv) and $CeCl_3$•$7H_2O$ (745 mg, 2.00 mmol, 1.4 equiv) were combined in 16 mL MeOH at 23 °C. After 20 min, the solution was cooled to 0 °C and $NaBH_4$ (76 mg, 2.0 mmol, 1.4 equiv) was added in several portions. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The material was purified by flash column chromatography, eluted with 4:1 hexanes/EtOAc, to give the reduced product as a 2:1 mixture of diastereomers of the allylic alcohol that were not separated. This mixture of diastereomers (347 mg, 1.23 mmol, 1 equiv) was added to a suspension of Pd/C (10%) (131 mg, 1.23 mmol, 0.1 equiv) in 14 mL MeOH and placed under an atmosphere of H_2 at 500 psi for 16 h. The solution was filtered through Celite®, washed with EtOAc (3 × 15 mL) and the combined organic phases were reduced *in vacuo*. Purification by flash column chromatography, eluting with 4:1 hexanes/EtOAc, afforded cyclopentanol **89** (350 mg, 76% 2:1 mixture; 227 mg, 49% **89**) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.28 – 7.19 (m, 3H), 6.77 – 6.66 (m, 2H), 6.55 – 6.46 (m, 2H), 4.21 (ddd, J = 13.4, 6.7, 6.7 Hz, 1H), 3.81 (ddd, J = 13.5, 7.5, 7.5 Hz, 1H), 3.73 (s, 3H), 2.85 (dd, J = 7.4, 7.4 Hz, 1H), 2.32 (dddd, J = 13.8, 7.4, 7.4, 7.4, Hz, 1H), 2.20 – 2.11 (m, 1H), 1.92 –

1.82 (m, 1H), 1.82 – 1.72 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4, 141.9, 141.1, 128.9, 127.8, 127.1, 115.4, 114.9, 78.9, 61.5, 60.4, 55.9, 32.5, 30.8 ppm; IR (thin film) 3377, 3028, 2952, 1602, 1512, 1237 cm^{-1}; MS (ESI) *m/z* 306.18 (306.15 calcd for $C_{18}H_{21}NO_2Na^+$ $[M + Na]^+$).

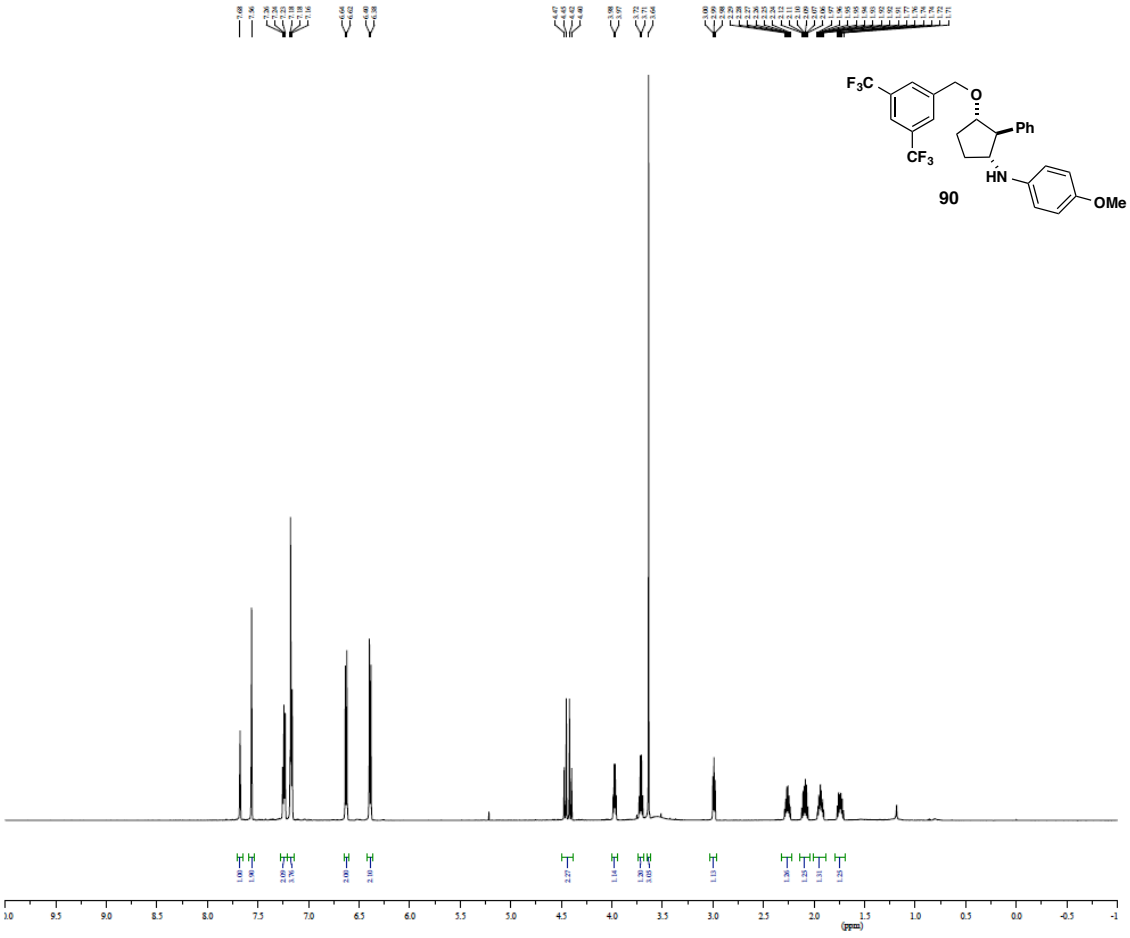


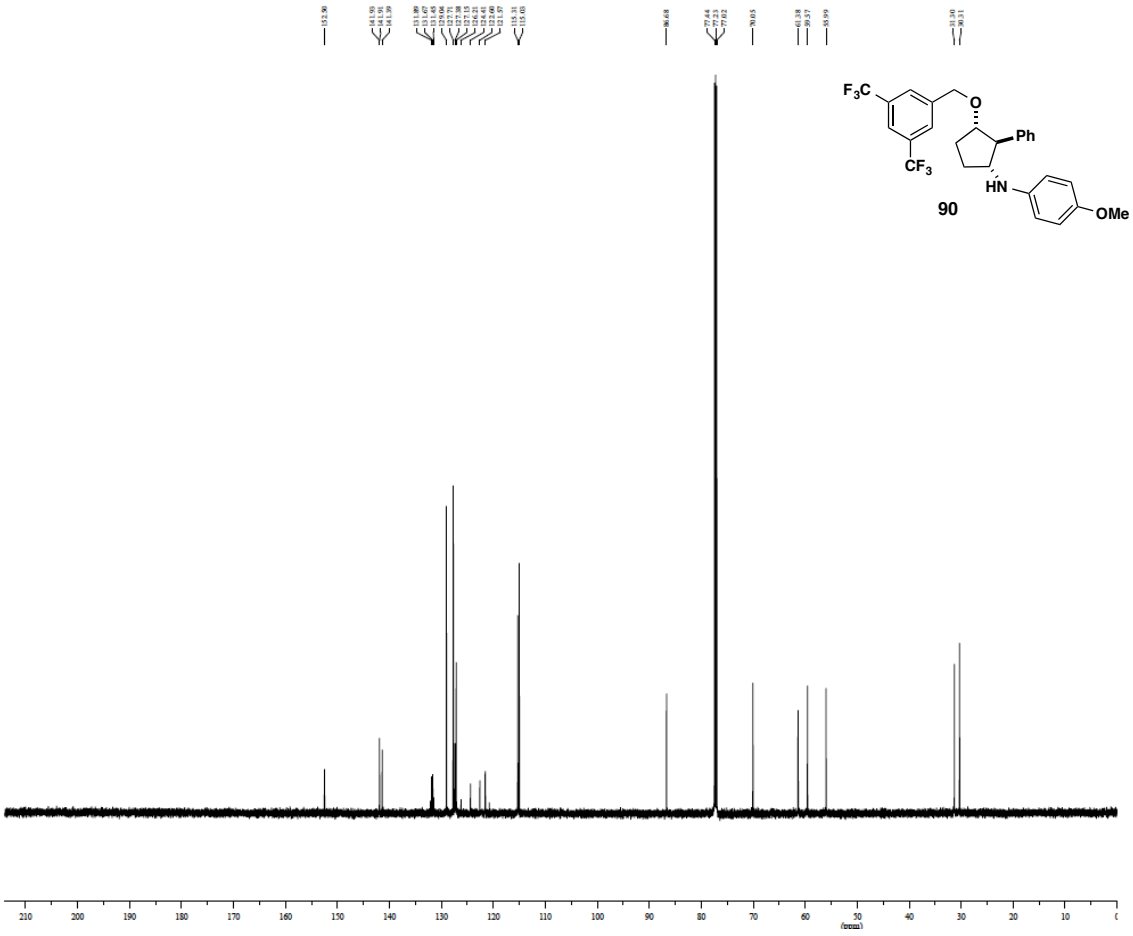


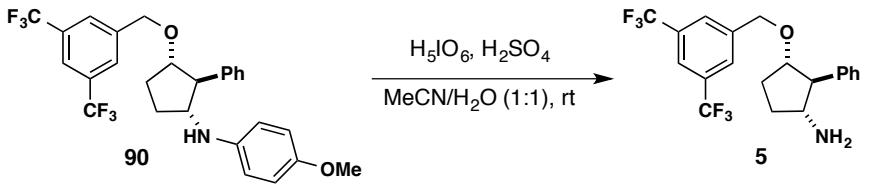


N-3-((3,5-bis(trifluoromethyl)benzyl)oxy)-2-phenylcyclopentyl)-4-methoxyaniline (90): Cyclopentanol **89** (111 mg, 0.39 mmol, 1 equiv) was added slowly to a suspension of NaH (168 mg, 7 mmol, 18 equiv) in 11 mL anhydrous THF under an atmosphere of N_2 and stirred for 1 h. Subsequently, 3,5-*bis*-trifluoromethylbenzyl bromide was added to the solution and the reaction was stirred at 23 °C for 16 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over $MgSO_4$, filtered and reduced *in vacuo*, then purified by flash column chromatography,

eluting with 9:1 hexanes/EtOAc, to afford **90** (149 mg, 75%) as a yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.66 (s, 2H), 7.36 – 7.31 (m, 2H), 7.28 – 7.24 (m, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.48 (d, *J* = 8.8 Hz, 2H), 4.53 (dd, *J* = 31.5, 12.8 Hz, 2H), 4.06 (ddd, *J* = 12.0, 6.1, 6.1 Hz, 1H), 3.80 (ddd, *J* = 14.3, 7.1, 7.1 Hz, 1H), 3.73 (s, 3H), 3.08 (ddd, *J* = 6.7, 6.7 Hz, 1H), 2.36 (dddd, *J* = 13.3, 7.0, 7.0, 7.0 Hz, 1H), 2.18 (dddd, *J* = 14.8, 7.6, 7.6, 7.6 Hz, 1H), 2.1 – 1.99 (m, 1H), 1.87 – 1.80 (dddd, *J* = 15.1, 7.5, 7.5, 7.5 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.5, 141.9, 141.9, 141.4, 131.8 (q, *J* = 33.2 Hz), 129.0, 127.7, 127.4 (m), 127.2, 123.5 (q, *J* = 272.2 Hz), 121.57 (ddd, *J* = 3.8, 3.8, 3.8 Hz),115.3, 115.0, 86.7, 70.1, 61.4, 59.6, 56.0, 31.3, 30.3 ppm; IR (thin film) 3030, 2937, 2834, 1622, 1512, 1352, 1280 cm^{-1}; HRMS (ESI) *m/z* 510.1844 (510.1868 calcd for $C_{27}H_{25}F_6NO_2H^+$ [M + H]$^+$).

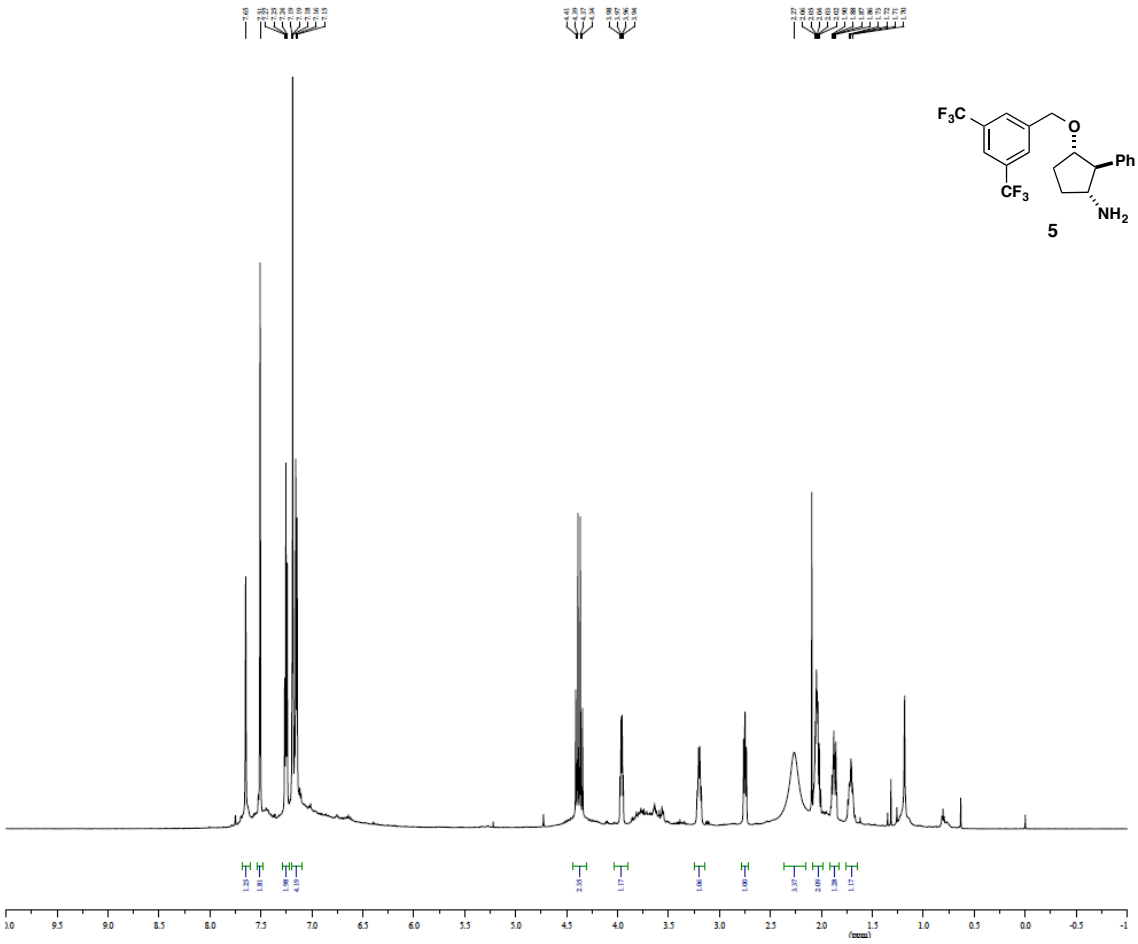


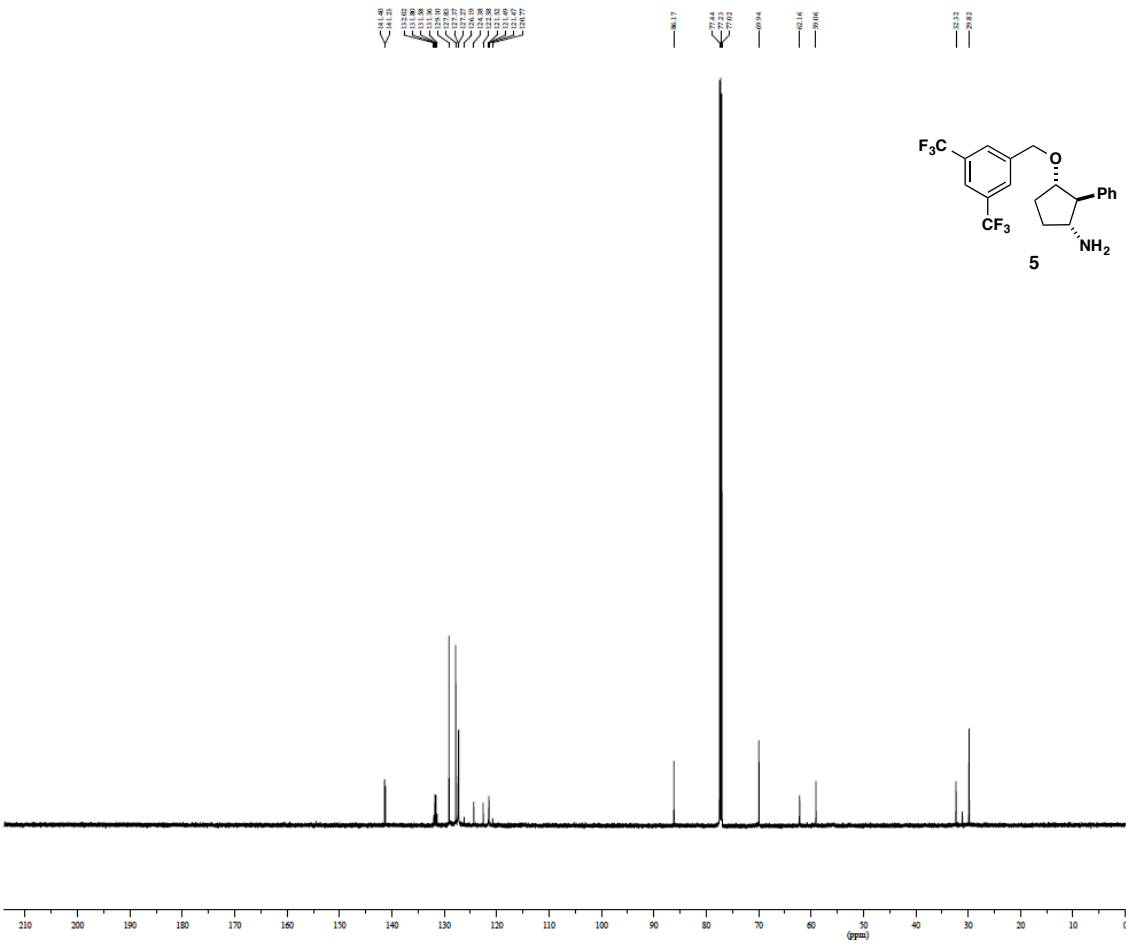




3-((3,5-bis(trifluoromethyl)benzyl)oxy)-2-phenylcyclopentanamine (5): To a solution of cyclopentane **90** (103 mg, 0.203 mmol, 1 equiv) in 4.4 mL MeCN/H_2O (1:1), H_5IO_6 (46.3 mg, 0.203 mmol, 1 equiv) and 1 M H_2SO_4 (203 μL, 0.203 mmol, 1 equiv) were added sequentially. The reaction mixture was stirred for 6 h at 23 °C. Upon completion, the solution was extracted with CH_2Cl_2 (3 × 10 mL). The aqueous phase was then adjusted to pH 10/11 using 5 M KOH and extracted with EtOAc (4 × 10 mL). The combined organic

layers were acidified to pH 1 with HCl/EtOAc, dried over $MgSO_4$, filtered and reduced *in vacuo*. The material was then purified by flash column chromatography, eluting with a gradient hexanes/EtOAc to 9:1 CH_2Cl_2/MeOH, to afford 3-((3,5-bis(trifluoromethyl)benzyl)oxy)-2-phenylcyclopentanamine **5** (47.5 mg, 58%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.59 (s, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.21 (m, 3H), 4.46 (dd, *J* = 26.9, 12.8 Hz, 2H), 4.04 (ddd, *J* = 12.3, 7.1, 7.1 Hz, 1H), 3.28 (ddd, *J* = 15.7, 9.2, 9.2 Hz, 1H), 2.83 (dd, *J* = 7.5, 7.5 Hz, 1H), 2.54 – 2.19 (bs, 2H), 2.17 – 2.07 (m, 2H), 2.00 – 1.92 (m, 1H), 1.85 – 1.73 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.4, 141.2, 131.8 (q, *J* = 33.3 Hz), 129.1, 127.8, 127.4 (m), 127.3, 123.5 (q, *J* = 272.4 Hz), 121.5 (dddd, *J* = 7.7, 3.7, 3.7, 3.7 Hz), 86.2, 69.9, 62.2, 59.1, 32.3, 29.8 ppm; IR (thin film) 3062, 3030, 2933, 1624, 1510, 1376, 1280, 1173 cm^{-1}; HRMS (ESI) *m/z* 404.1434 (404.1449 calcd for $C_{20}H_{19}F_6NOH^+$ $[M + H]^+$).


F3C
O
Ph
CF3
NH2
5


F3C
O
Ph
CF3
NH2
5
(ppm)

3. Dysprosium Trifluoromethanesulfonate Catalysis

3.1. Rare Earth Lewis Acid Catalysis

Following the development of a dysprosium catalyzed aza-Piancatelli rearrangement, we wanted to address the choice of catalyst in more detail and provide insight on the potential of dysprosium triflate, and rare earth triflates in general, as versatile catalysts.

Within this chapter, the merits and potential of dysprosium will be highlighted based on a review and an e-EROS article we authored to create a knowledge base and generate interest in this catalyst in the synthetic community.[89,90]

The chemistry of rare earth (lanthanide) Lewis acids has received increasing attention from the synthetic community since their initial use as shift reagents.[91–95] Thanks to intensive studies by Kobayashi[94–96] and others,[97] lanthanides have since found widespread use as mild, stable Lewis acids that are known for their oxophilicity and stability in aqueous media, making them water-compatible Lewis acids. These qualities combined with recyclability, low toxicity and a moderate price makes lanthanide catalysis attractive, especially in terms of sustainability.

The rare earth elements possess a gradual variation in physical properties that result in many examples where the efficacy varies only slightly from one reaction to another.[95,98,99] The similar reactivity patterns have caused synthetic chemist to focus predominantly on scandium and ytterbium, the two rare earth elements with the highest Lewis acidity. As a result little is known about the possible advantages or disadvantages of the other members of the lanthanide family. An existing challenge in reaction development with lanthanide Lewis acid catalysts is predictability and a clear understanding of when or why particular rare earths promote a certain transformation. Exploring the reactivity of the other lanthanides

will undoubtedly lead to a better understanding of these catalysts and hopefully also result in new reaction development.

3.2. About Dysprosium

Our group became highly intrigued by difficult to pronounce dysprosium, after discovering Batey's success with the metal in his synthesis of 4,5-diaminocyclopentenones.[40] The word dysprosium originates from the Greek *dysprositos*, meaning hard to get at, and element 66 holds true to its name. First discovered in 1886 by Lecoq de Boisbaudran, dysprosium was not isolated in its pure form until almost a century later, in 1950.[5] The metal has not received much attention from the synthetic community even though, compared to other lanthanides, dysprosium exhibits similar stability to air and water, ease of handling, Lewis acidity and oxophilicity.

The basic properties of dysprosium are outlined in Figure 3.1.[91–95,98,99] Analogous to the other lanthanides, dysprosium (III) is the most stable oxidation state. Dysprosium resides after the gadolinium break and has an extended Xe-core electronic configuration, $[Xe]4f^9$. The ionic radius and therefore its intrinsic Lewis acidity (Lewis acidity = Z/r^3; Z= charge and r = ionic radius) are just below scandium and ytterbium and very similar to the surrounding elements Tb, Ho, Er, Tm and Lu. Dysprosium is the cheapest element in the Tb–Lu series but comparable in price to ytterbium.[100] The number of ligands coordinated to dysprosium is often between 8 and 9.[101] Unlike *d*-transition metals, however, ligand bonding such as σ-donor/π-acceptor interactions, the 18-electron rule, and the formation of double or triple bonds are not observed with dysprosium(III) or in other lanthanide(III) chemistry.

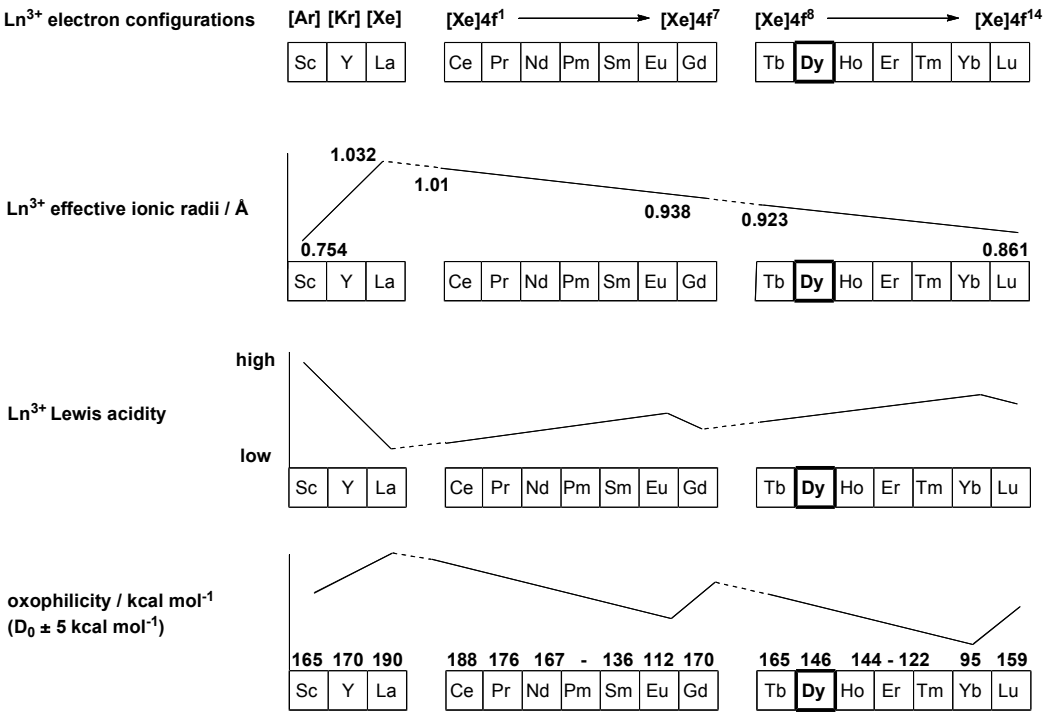


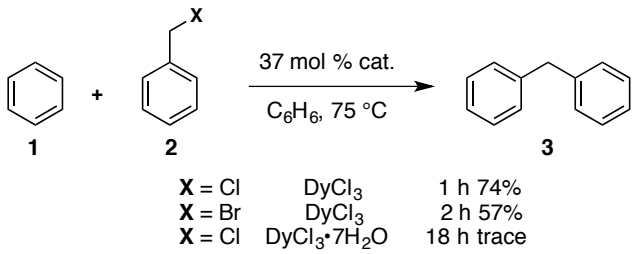
Figure 3.1. Characteristic features of lanthanide ions and elements. D_0 = dissociation energy of the Ln–O bond.

Due to its mild nature, dysprosium is an excellent catalyst for multicomponent reactions where both nitrogen and oxygen functionalities are present. Importantly, the metal retains its catalytic activity in the presence of Lewis basic nitrogen groups, allowing for its use in a variety of transformations with unprotected amines. Dysprosium triflate is commercially available, but may also be prepared by treatment of its oxide with aqueous triflic acid.[102] Many transformations with dysprosium can be achieved in protic media and ionic liquids and the catalyst can be recycled, making dysprosium a suitable catalyst for applications in green chemistry. The following section is a nearly extensive list of reports that focused on reaction development with dysprosium.

3.3. Organic Chemistry with Dysprosium

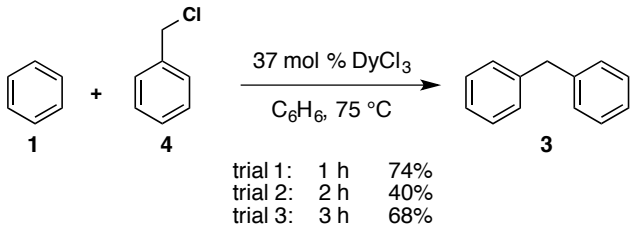
3.3.1. Dysprosium Catalyzed Friedel–Crafts Alkylation

Alkylation reactions are crucial for carbon-carbon bond formation, and the Friedel–Crafts alkylation, initially reported in 1877, deservedly still receives attention from synthetic chemists as a means to establish essential carbon-carbon bonds.[103] In 1986, Fujiwara and co-workers reported the use of lanthanide chlorides ($LnCl_3$) in the Friedel–Crafts alkylation of arenes.[104] The heterogeneous reaction proceeded with the arene as the solvent using 37 mol % of the $LnCl_3$ relative to the alkyl halide. Screening of all lanthanide chlorides, with the exception of radioactive promethium(III) chloride, revealed that the late lanthanides were more effective catalysts than the early rare earths. It is important to note that the hydrated $LnCl_3 \bullet xH_2O$ (x = 6, or 7) was an ineffective catalyst, producing only trace amounts of product after 18 h compared to 74% after 1 h when the catalyst was dried by heating at 150 °C under vacuum for 2 h (Scheme 3.1). Dysprosium was highlighted as the optimal alkylation catalyst.



Scheme 3.1. Dysprosium catalyzed Friedel–Crafts alkylation.

The catalyst can easily be recovered and recycled, maintaining catalytic activity over three reaction cycles (Scheme 3.2). This method is one of the few examples of $DyCl_3$ as a catalyst, as the rare earth chlorides often are not included in catalyst screening or show no catalytic activity. The scope of the reaction is limited, extending only to benzene and toluene arene partners.

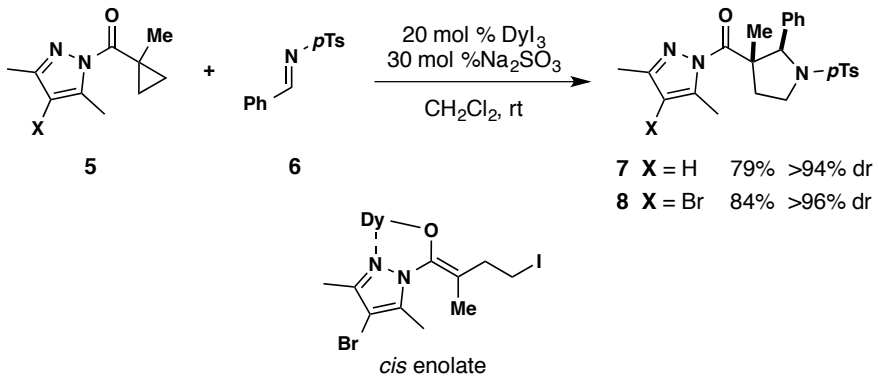


Scheme 3.2. Recycling of the dysprosium catalyst.

3.3.2. Dysprosium Catalyzed Mannich-Type Reactions

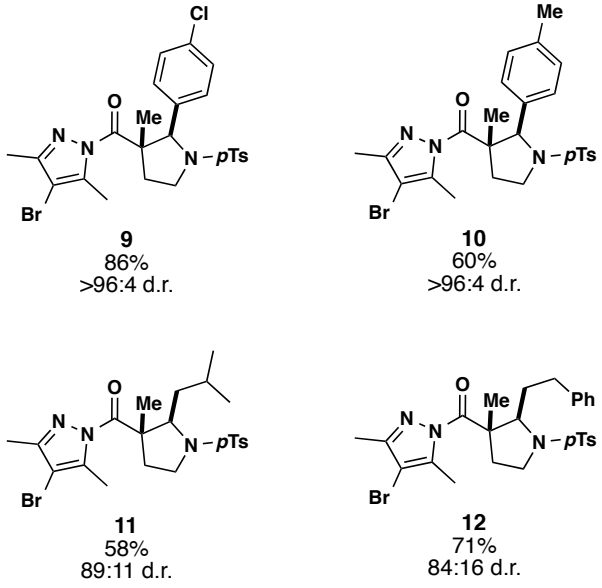
Widely used as a valuable transformation in total synthesis, the Mannich reaction is an important target in method development and is particularly useful when stereocenters are set during the transformation under mild reaction conditions.[105–107]

The unusual use of DyI_3 as catalyst for a Mannich-type addition of imines to α,α-disubstituted enolates, generated from a cyclopropane ring opening, to access pyrrolidines containing all-carbon quaternary stereocenters was detailed by Matsunga and Shibasaki and co-workers.[108] Use of 20 mol % DyI_3 was the most effective Lewis acid catalyst loading and addition of 30 mol % Na_2SO_3 could enhance the yield from 66 to 79% without affecting the excellent >96:4 diastereomeric ratio (Scheme 3.3). This additive is speculated to generate a reducing medium in which the detrimental formation of I_2 is suppressed. Use of the 4-bromo-3,5-dimethylpyrazole analogue allowed for an additional increase in yield to 84%. Conversion of the *N*-acyl pyrazole group of **8** to the methyl ester was achieved in high yield when using $Er(OTf)_3$ in MeOH at 50 °C in 93% yield.



Scheme 3.3. DyI_3 catalyzed Mannich reaction.

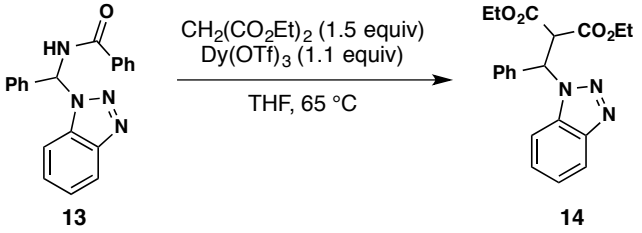
In addition to a variety of substituted aryl imines, where electron-poor substrates performed better than their electron-rich counterparts, Matsunga and Shibasaki and co-workers were also able to extend the methodology to alkyl imines (Scheme 3.4). The high diastereoselectivity is believed to stem from preferred formation of the *cis*-enolate depicted in Scheme 3.3.



Scheme 3.4. Scope of the DyI_3 catalyzed Mannich reaction.

A method for the synthesis of benzotriazole derivatives from *N*-(α-benzotriazolyl-alkyl)amides was developed by Fan and co-workers.[109] After screening a variety of Lewis

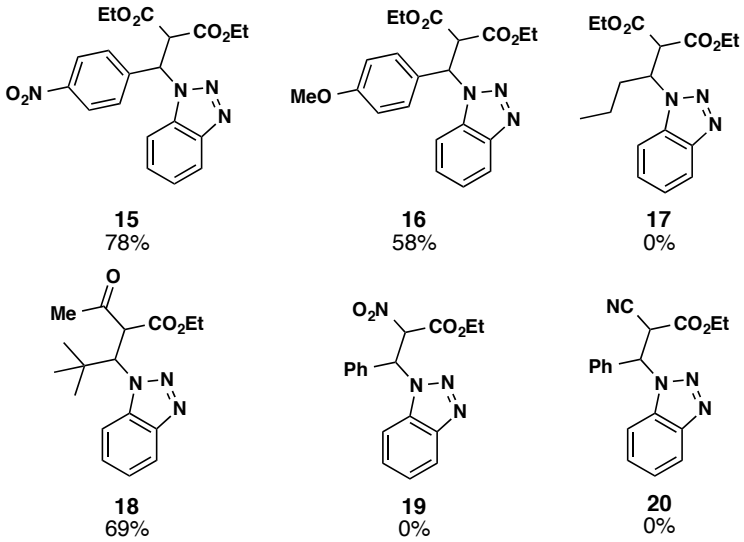
acids, $Dy(OTf)_3$ was identified as the Lewis acid capable of promoting transformation to the desired compound **14**, reported to have fungicidal activity (Scheme 3.5). Using less than one equivalent of $Dy(OTf)_3$ did not promote the reaction. However, the authors found that the addition of benzotriazole could increase the yield from 51 to 78% in THF.



13 **14**

Scheme 3.5. Dysprosium catalyzed synthesis of benzotriazole derivatives.

Regarding the substrate scope of the transformation, Fan and co-workers found that electron-poor substrates produced higher yields compared to electron-rich starting materials, and that use of aliphatic substrates was unsuccessful under the reaction conditions (Scheme 3.6, **15–17**). Varying the nucleophile, methyl- (**18**) or ethyl-3-oxobutanoate (not shown) also participated in the reaction in good yield, but ethyl-2-nitroacetate (**19**) or ethyl-2-cyanoacetate (**20**) were ineffective nucleophiles.

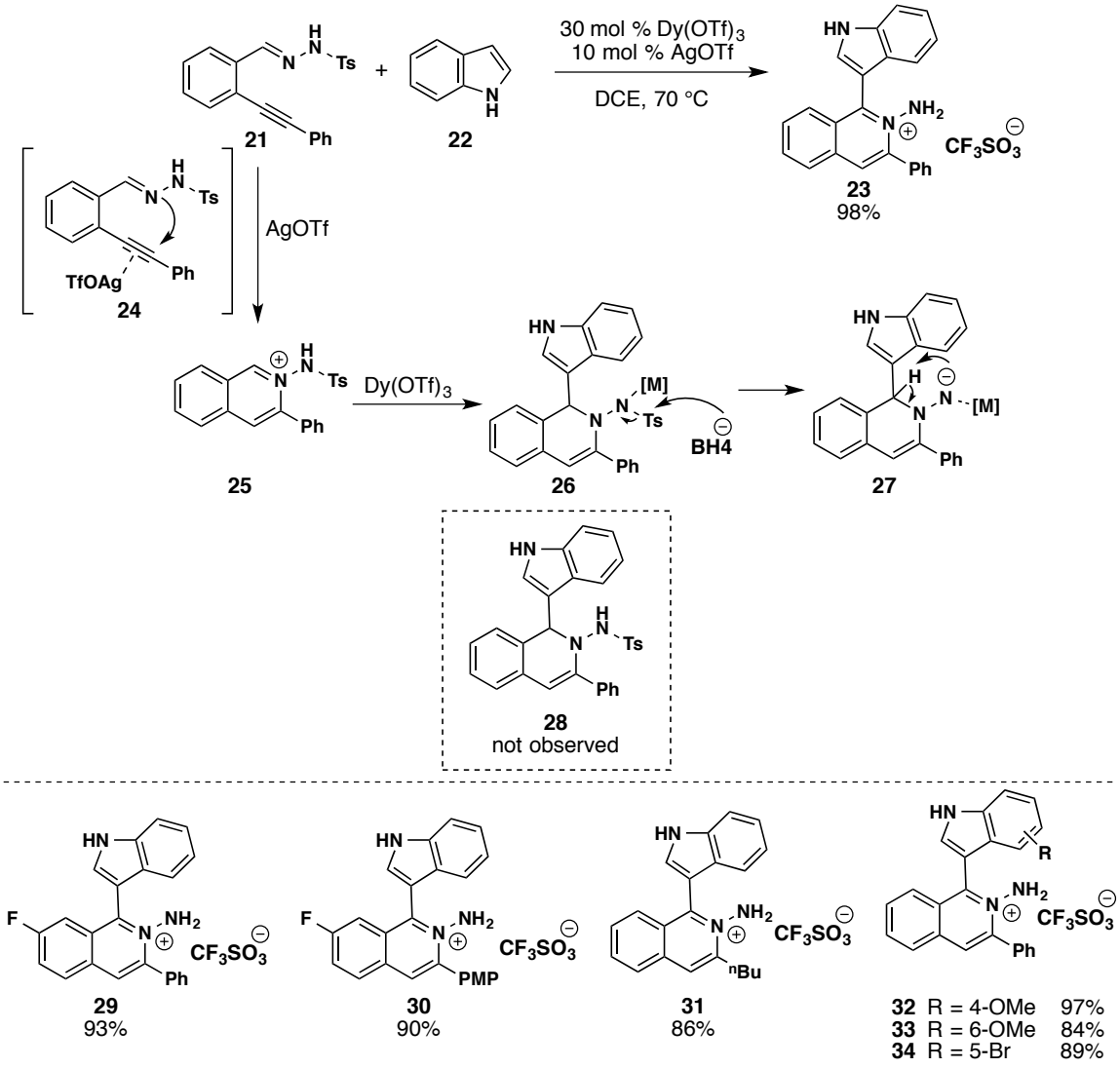


15 78% **16** 58% **17** 0%

18 69% **19** 0% **20** 0%

Scheme 3.6. Scope of the benzotriazole synthesis.

In 2009, Wu and co-workers reported the use of a AgOTf/$Dy(OTf)_3$ catalyst system to synthesize 1-(indol-3-yl)-2-aminoisoquinolinium triflates that relied on a Mannich-type reaction.[110] This transformation allowed access to a range of substituted indoles. Present in a large number of natural products and biologically active molecules, the indole structural motif is a prominent target in methodology and total synthesis.[111]



Scheme 3.7. Proposed reaction mechanism and scope for Wu's Mannich type reaction.

Use of AgOTf in 1,2-dichloroethane (DCE) at 70 °C gave the 6-endo cyclization product **25** in 99% yield but the desired product, **28** was not observed (Scheme 7). Use of $Dy(OTf)_3$

and other Lewis acids produced only small amounts of **25**. Significantly, the authors found that reaction of **25** with indole catalyzed by $Dy(OTf)_3$ in MeCN produced **23** in 28% yield (the initially proposed product **28** was not observed). Driven by these results, the investigation of a tandem catalytic reaction using AgOTf and $Dy(OTf)_3$ led to the development of the multicatalytic methodology. The one-pot, three step reaction proceeded in good yield via a silver-catalyzed intramolecular cyclization followed by dysprosium-catalyzed nucleophilic addition of indole, and finally elimination of the sulfonyl group, affording unexpected 1-(indol-3-yl)-2-aminoisoquinolinium triflates. A multicatalytic reaction that provides the possibility of accomplishing numerous transformations in one pot makes this transformation a powerful synthetic tool.[112,113]

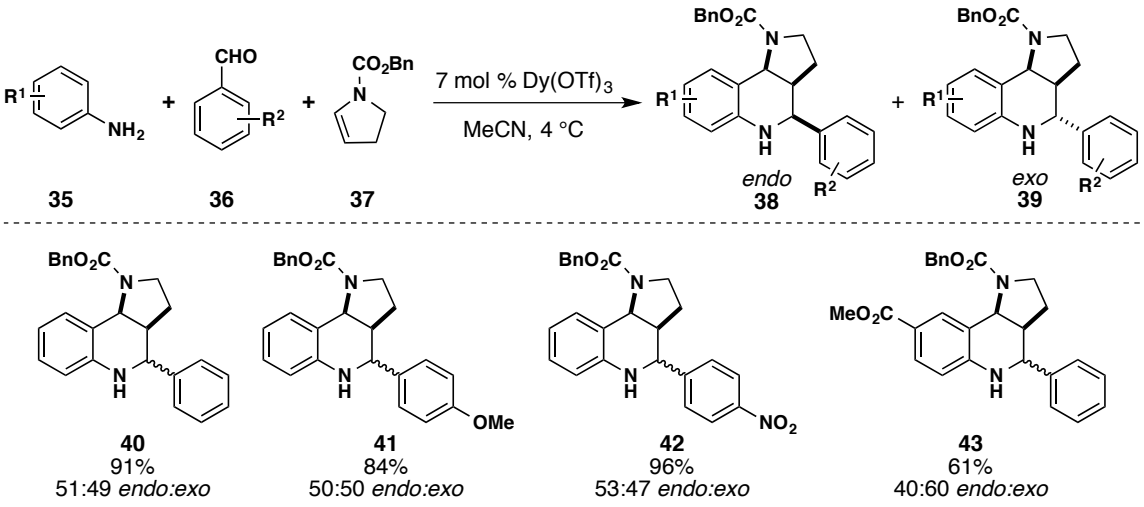
A fluorine substituent on the aryl ring (**29**) decreased the yield slightly to 93%, and exchange of phenyl for a *p*-methoxyphenyl group (**30**) on the acetylene reduced the yield to 90% (Scheme 3.7). Even alkyl groups on the acetylene (**31**) and a variety of substituents on the indole portion were tolerated (**32–34**).

3.3.3. Dysprosium Catalyzed Diels–Alder and Povarov Reaction

The Diels–Alder reaction has long been recognized as a powerful reaction with a rich history in the synthesis of natural and unnatural carbocycles and heterocycles.[114,115] The Povarov reaction, an imino variant of the Diels–Alder cycloaddition provides a direct route to different nitrogen heterocycles from readily available Schiff bases.[116] There has been a renewed interest in the Povarov reaction since Kobayashi and co-workers demonstrated that lanthanide triflates, specifically $Yb(OTf)_3$, catalyze the reaction of cyclopentadiene or dihydrofuran (DHF) with *in situ* formed imines.[117]

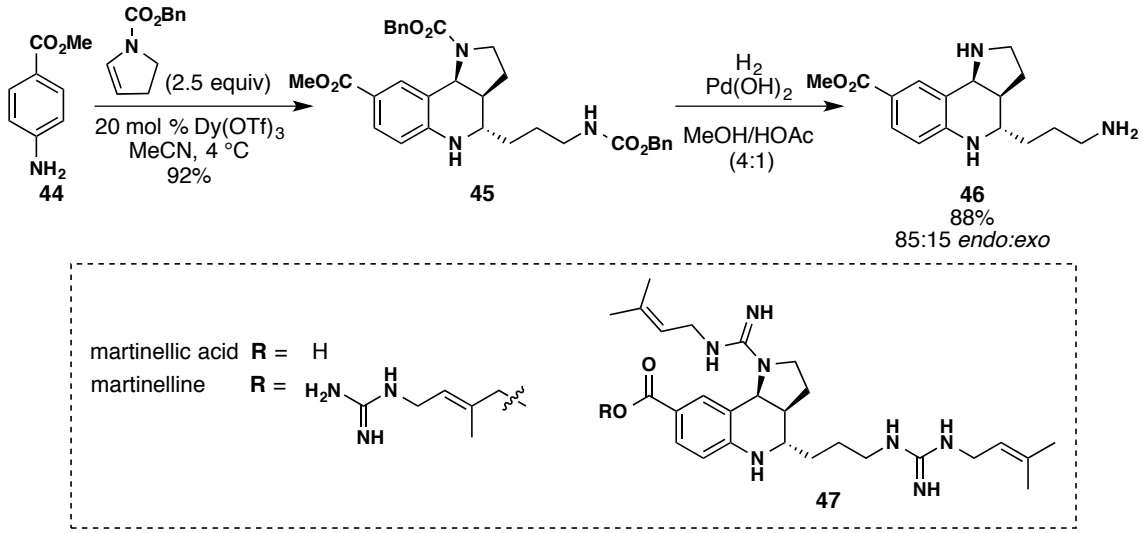
In efforts toward the total synthesis of the alkaloids martinelline and martinellic acid (**47**), Batey and co-workers developed a three-component coupling of anilines,

benzaldehydes and *N*-substituted-2-pyrrolidine to access substituted hexahydropyrrolo[3,2-*c*]-quinolines (Scheme 3.8).[118] The favored catalyst for this reaction was $Dy(OTf)_3$ in MeCN, although yields were only marginally better compared to other rare earth triflates.



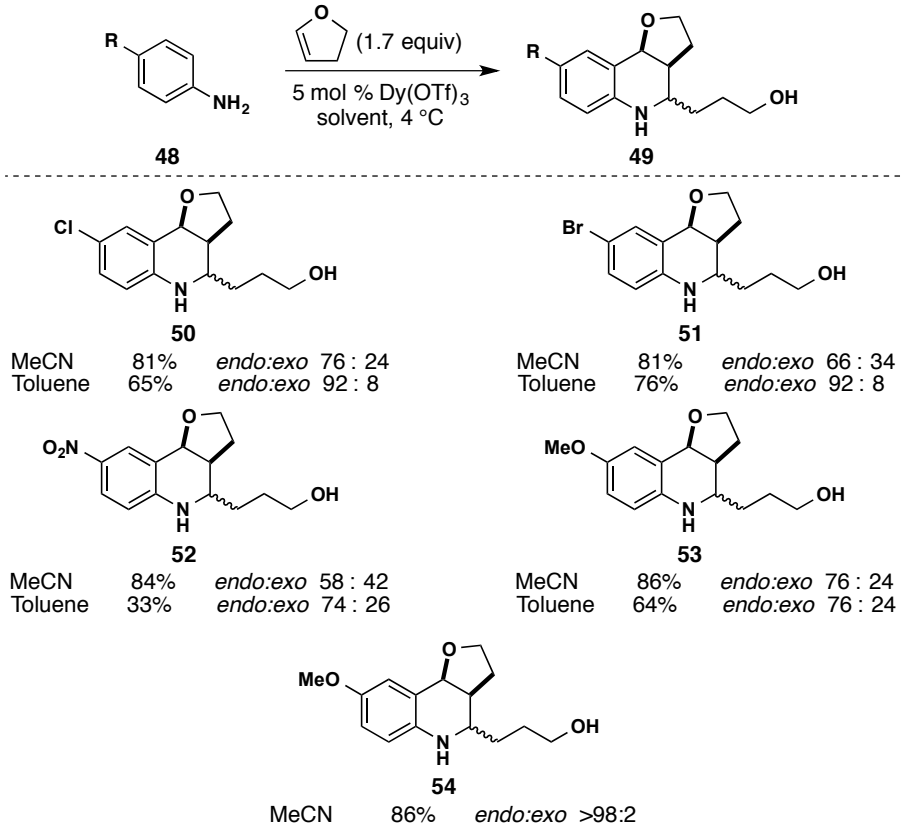
Scheme 3.8. Scope of Batey's three-component coupling reaction.

The proposed mechanism proceeds through the complexation of the imine, formed *in situ* via condensation of the aldehyde and aniline. Stepwise nucleophilic addition of the pyrrolidine and ring closure by electrophilic aromatic substitution then affords the product. In addition, Batey and co-workers found that a 2:1 coupling of enamine and aniline gave **45** as mainly the *endo* diastereomer (Scheme 3.9). Using water as the co-solvent, the *endo*-product was favored, presumably due to the hydrophobic effect that would favor a more compact transition state. In the published total synthesis of martinelline **47**, Batey and co-workers resorted to the use of camphorsulfonic acid as they were unable to obtain the desired *exo* diastereomer using Lewis acids.[119]



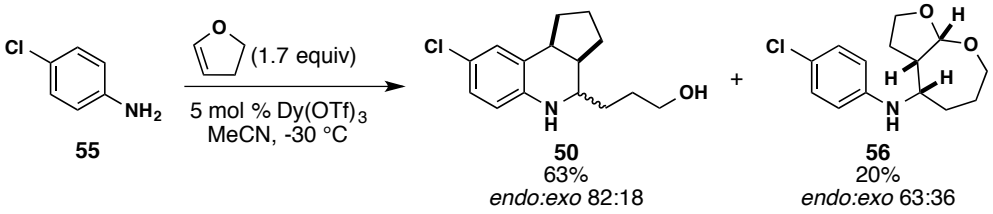
Scheme 3.9. Selective formation of the *endo* isomer.

In a subsequent report, Batey and co-workers described the 2:1 coupling of DHF with anilines catalyzed by $Dy(OTf)_3$.[120] The reaction of 4-chloroaniline with DHF proceeded well in MeCN giving approximately a 3:1 mixture of *endo*:*exo* diastereomers (Scheme 3.10). At a detriment to the yield, the *endo*:*exo* ratio could be greatly improved to 92:8 when performed in toluene. It is worth noting that $DyCl_3 \bullet 6H_2O$ (5 mol %) also catalyzed the reaction to afford a 64:36 ratio of *endo*:*exo* products in 78% yield; a rare example of a reaction with dysprosium(III) chloride. The trend of increased *endo* selectivity in toluene held true for a variety of anilines with the exception of *p*-methoxyanline **53** where no effect was noted. Interestingly, use of methyl-4-aminobenzoate led to product **54** in a >98:2 *endo*:*exo* ratio in MeCN.



Scheme 3.10. Batey's 2:1 coupling of DHF with anilines.

In an attempt to increase the diastereomeric ratio, the effect of temperature was tested. At lower temperatures, oxepin **56** was formed. However, oxepin **56** rearranged to the *exo*-diastereomer when resubjected to the reaction conditions at rt, such that, ultimately, the *endo*:*exo* ratio was not affected by temperature (Scheme 3.11).



Scheme 3.11. Effect of temperature on the reaction.

The mechanism of the reaction could proceed via a concerted or stepwise process, and it could change depending on the solvent. Batey and co-workers propose that, due to the

formation of the oxepin at lower temperatures, at least a partially stepwise mechanism is plausible (Figure 3.2).

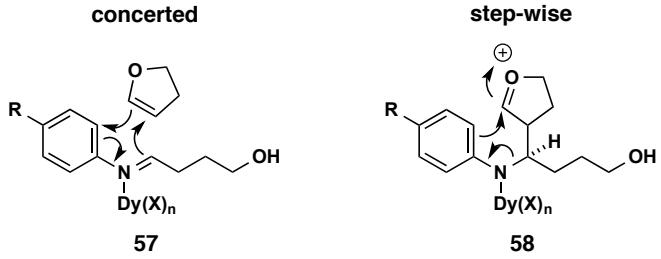
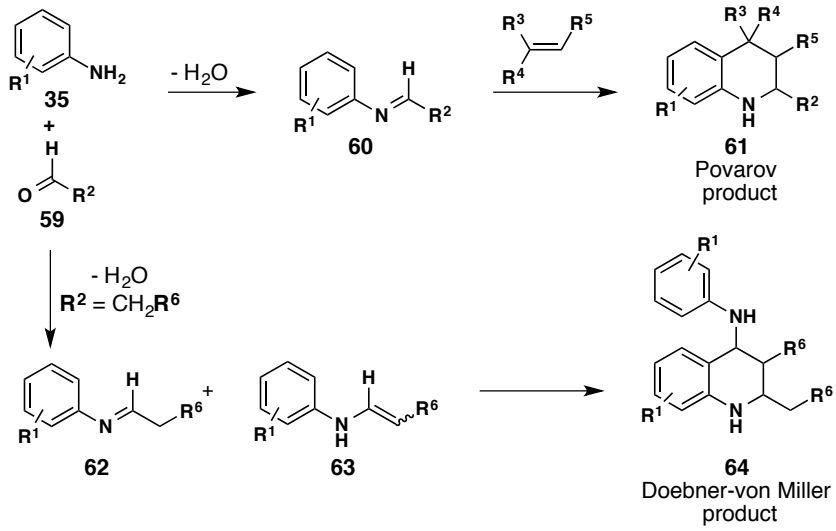
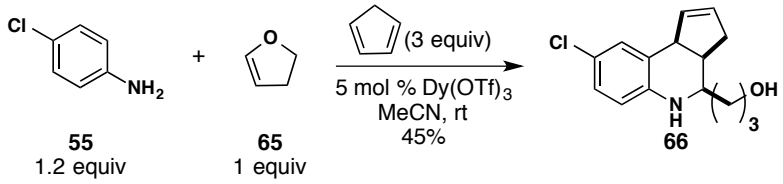


Figure 3.2. Depiction of both concerted and stepwise mechanisms.

Although a three-component coupling had successfully been developed for the Povarov reaction with aldehydes lacking α-protons, the use of aliphatic aldehydes with enolizable protons was limited to only a few examples.[121,122] However, following the exploration of the 2:1 coupling of DHF and anilines,[120] Batey and co-workers developed a three-component coupling of aniline with cyclopentadiene and aliphatic aldehydes containing enolizable protons and their synthetic equivalent (Scheme 13–15).[123] Reaction conditions had to be adjusted such that the competing Doebner-von Miller product would not be observed (Scheme 3.12). The competing 2:1 coupling with DHF was minimized by slow syringe-pump addition of DHF to afford the desired product.

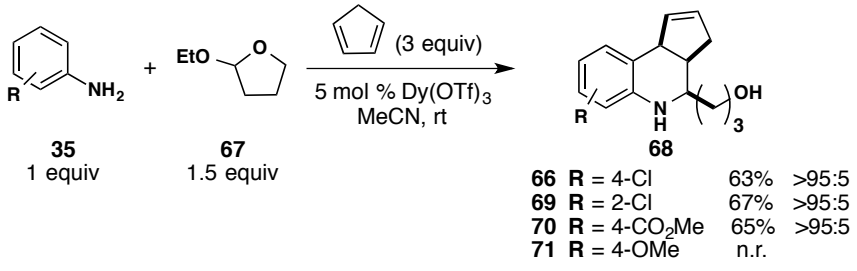


Scheme 3.12. Competing reactions in three-component coupling reactions.



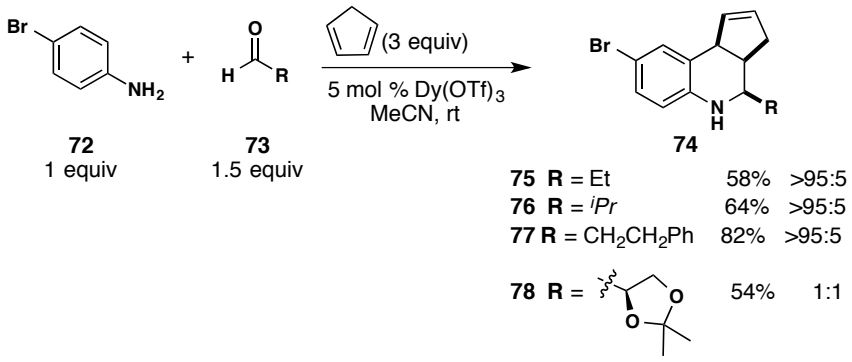
Scheme 3.13.

Use of 2-ethoxytetrahydrofuran allowed for further reduction of the undesired 2:1 coupling and gave **68** in 63–67% yield and >95:5 diastereomeric ratio (Scheme 3.14). A variety of substituted anilines participate in the reaction with the exception of *p*-methoxy aniline (**66**, **69**–**71**).



Scheme 3.14.

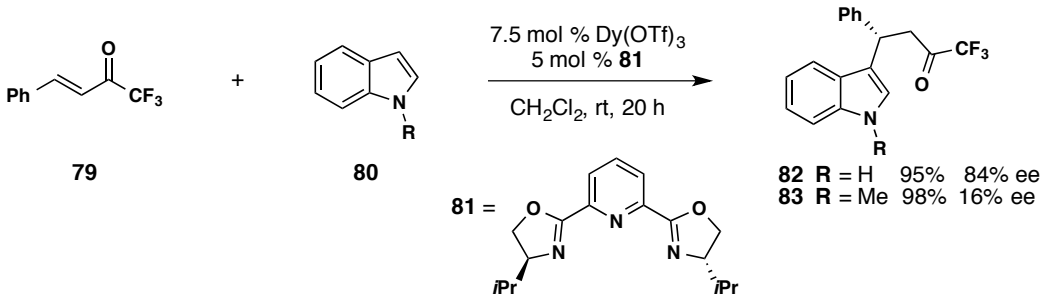
Taking advantage of the mild reaction conditions and employing the slow-addition protocol, aliphatic aldehydes, such as ethyl and isopropyl aldehyde could be used with high selectivity in the three-component Povarov reaction (Scheme 3.15).



Scheme 3.15.

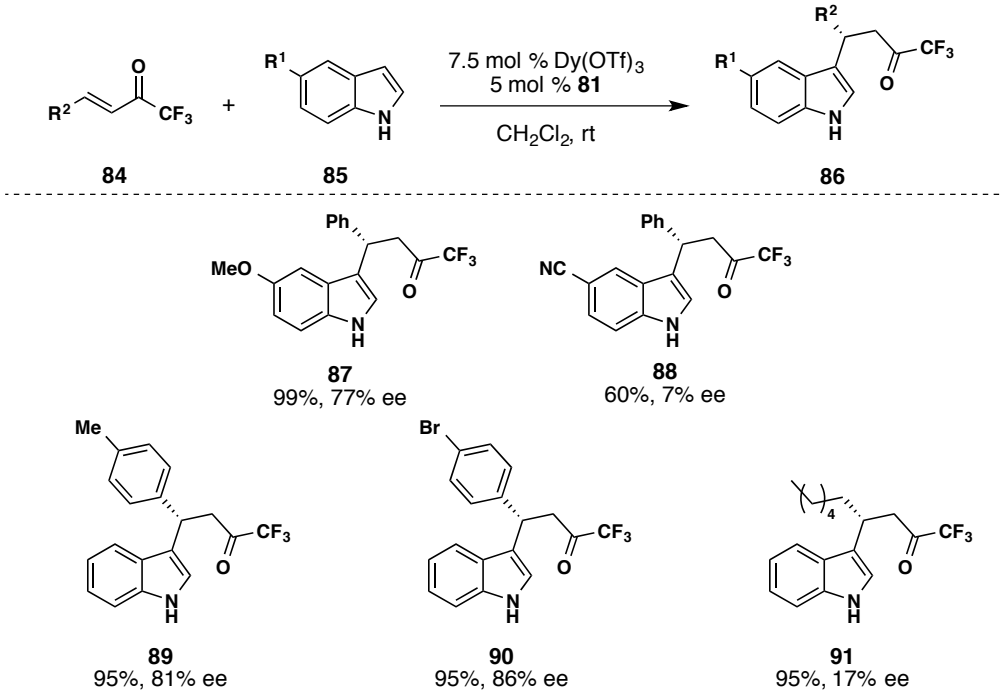
3.3.4. Enantioselective Dysprosium Catalyzed Alkylation

A rare enantioselective alkylation of indoles with α,β-unsaturated trifluoromethyl ketones was developed by Higashiyama and co-workers who reported use of a $Dy(OTf)_3$•PyBox catalyst system.[124] Initial screening of Lewis acids indicated $Sc(OTf)_3$ as a suitable catalyst with a follow-up screen of lanthanide trifluoromethanesulfonates identifying $Dy(OTf)_3$ to be the optimal catalyst producing **82** in 95% yield and 84% ee (Scheme 3.16). Although *N*-alkylated indoles participated in the reaction in good yield, enantioselectivity was greatly affected, suggesting an interaction of the indole nitrogen with dysprosium during the stereodefining event (N-H, 84% ee, N-Me, 16% ee). In contrast to many other rare earth metal catalyzed reactions, ytterbium and lanthanum were ineffective catalysts for this alkylation reaction.



Scheme 3.16. Dysprosium catalyzed enantioselective alkylation.

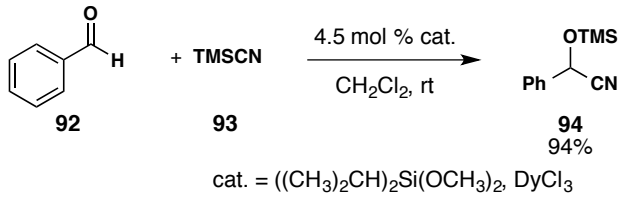
Varying substitution at the C5-position of the indole established a trend of increased yield and selectivity for electron-donating substituents compared to electron-withdrawing substituents. The scope of α,β-substituted trifluoromethyl ketones included electron-withdrawing substituents with little effect on yield and selectivity, but greatly decreased selectivity for aliphatic groups (Scheme 3.17).



Scheme 3.17. Scope of the enantioselective alkylation reaction.

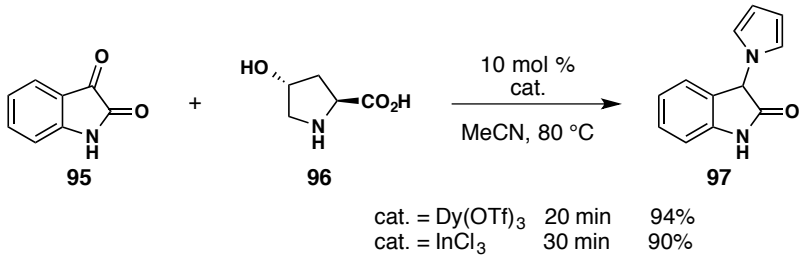
3.3.5. Other Dysprosium Catalyzed Reactions

Mei and co-workers investigated the synthesis of cyanohydrins from aldehydes and TMSCN catalyzed by a alkyldimethoxysilane dysprosium complex.[125] The reaction of benzaldehyde with TMSCN using 4.5 mol % dysprosium catalyst afforded the cyanohydrin **94** in 94% yield (Scheme 3.18). When substituted in the 2- and 4-position, 2-substituted aryl aldehydes were more reactive than 4-substituted aryl aldehydes.



Scheme 3.18. Dysprosium catalyzed cyanohydrin synthesis.

In a comparative study of $Dy(OTf)_3$ and $InCl_3$, Yadav and co-workers studied the formation of 3-pyrrolyl-indolines and pyrrolyl-indeno[1,2-*b*] quinoxalines.[126] A coupling of isatins with 4-hydroxyproline catalyzed by 10 mol % $Dy(OTf)_3$ allowed for the synthesis of *N*-substituted pyrroles in good to excellent yields under neutral conditions (Scheme 3.19 and Scheme 3.20).

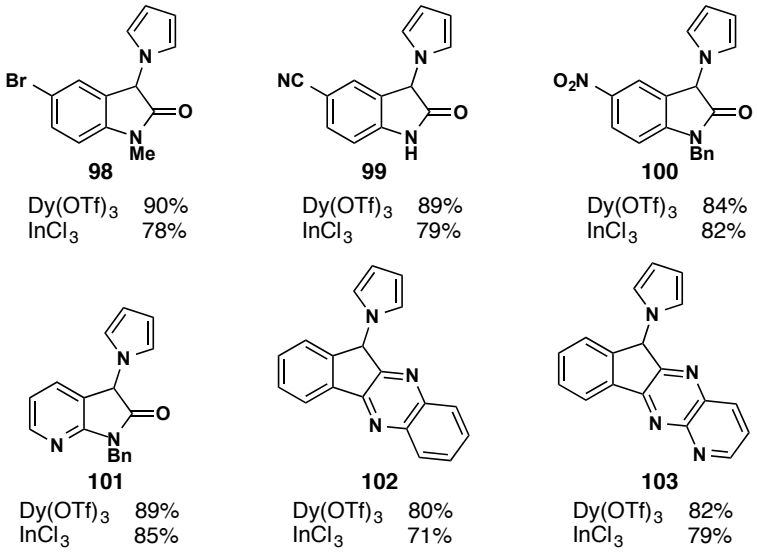


Scheme 3.19. Comparative study with $Dy(OTf)_3$ and $InCl_3$.

The reaction worked best in MeCN, but similar yields could be achieved in water at a sacrifice of reaction time. One limitation of this method is that simpler 1,2-diketones did not participate in the reaction due to the requisite stabilization provided by the zwitterionic

intermediate of the α-ketoamido functionality of the diketone. Interestingly, 11*H*-indeno[1,2-*b*]quinoxalin-11-one derivatives also participated in the reaction to afford 11-(1*H*-pyrrol-1-yl)-11*H*-indeno[1,2-*b*]quinoxalin-11-ones in good yield (Scheme 3.20, **102** and **103**).

Other lanthanides, such as $Y(OTf)_3$, $Ce(OTf)_3$, $Sm(OTf)_3$ and $Gd(OTf)_3$, were tested but their performance was inferior to $Dy(OTf)_3$. Indium trichloride was an effective catalyst for the transformation, but produced slightly lower yields and due to its lower cost, $Dy(OTf)_3$ is the preferred catalyst.



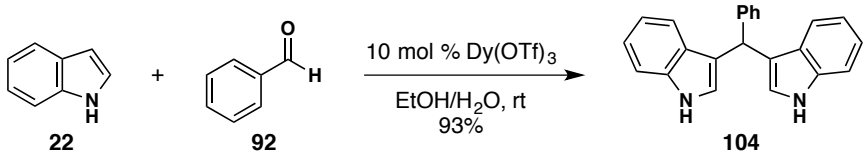
Scheme 3.20. Scope of the comparative study with $Dy(OTf)_3$ and $InCl_3$.

3.3.6. Dysprosium in Protic Media

A prominent feature of lanthanides is their stability and activity in protic media, making them ideal catalysts for green chemistry.[96,127,128] Wang and co-workers made use of this feature, exploring the use of lanthanides as stable Lewis acids in water.[129] They reported the use of $Ln(OTf)_3$ catalysts for the reaction of indoles with both aldehydes and ketones in protic systems. A test of various lanthanides established $Dy(OTf)_3$ as the optimal catalyst.

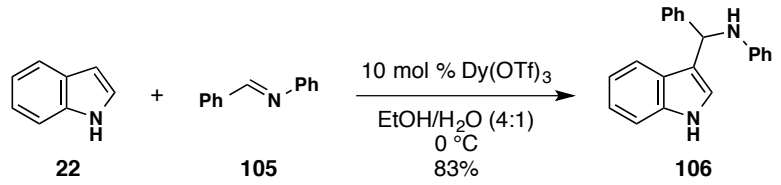
The reaction of indole with benzaldehyde in EtOH/H_2O (3:1 v/v) proceeded in 93% yield at room temperature, using 10 mol % of $Dy(OTf)_3$ catalyst (Scheme 3.21).

Additionally, the catalyst is recyclable and control experiments using NaOTf and $Mg(OTf)_2$ show that dysprosium is likely to be involved in the catalytic process and is necessary to promote the transformation.



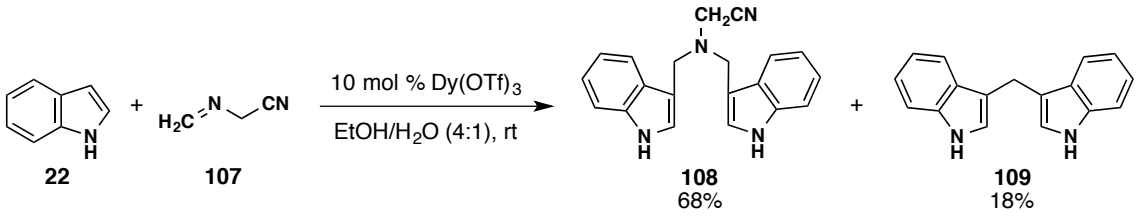
Scheme 3.21. Dysprosium catalyzed reaction of indoles and aldehydes in protic media.

Expanding on their publication, Wang and co-workers described the reaction of indole with imines in protic media.[130] The reaction of *N*-benzylidene aniline with indole to afford 3-(phenylamino benzylidene) indole was catalyzed by 10 mol % $Dy(OTf)_3$ in EtOH/H_2O (4:1) (Scheme 3.22). The range of $Ln(OTf)_3$ catalysts tested showed Yb and Dy to be the most effective catalysts, and $Dy(OTf)_3$ was chosen for reaction development.



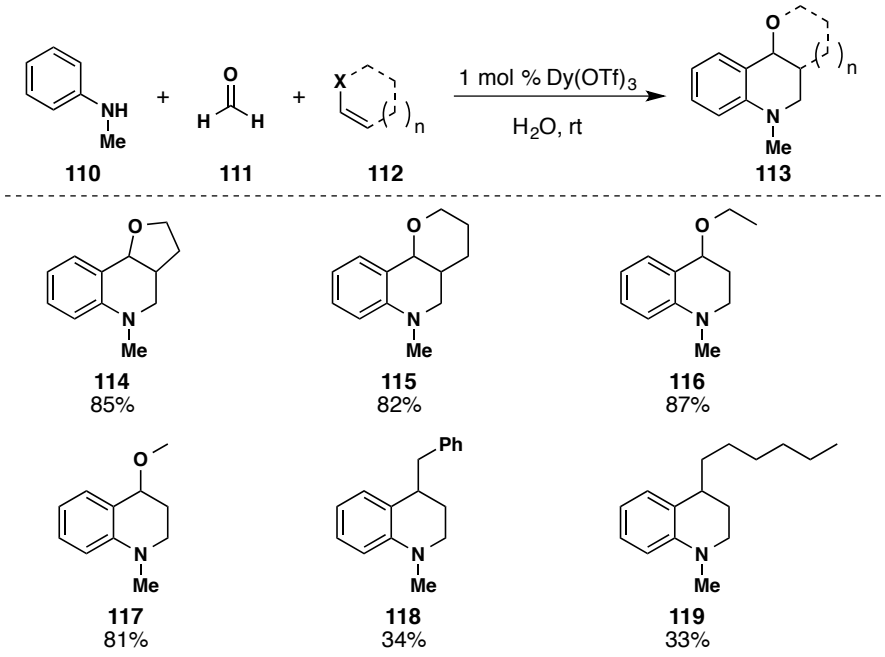
Scheme 3.22. Dysprosium catalyzed reaction of indole and an imine in aqueous medium.

Interestingly, the reaction of indole with methylene aminoacetonitrile gave **108** and **109** as the sole products (Scheme 3.23). Presumably, these products stem from the generation of formaldehyde from *in situ* hydrolysis to form an iminium ion. Subsequent Mannich reaction with the indole affords the observed products. Unfortunately, a three-component coupling reaction of indole, benzaldehyde and aniline proved unsuccessful, resulting only in the formation of phenyl bisindolylmethane.



Scheme 3.23. Dysprosium catalyzed reaction of indole with methylene amino-acetonitrile in aqueous medium.

In 2002, Chen and Quian reported the $Dy(OTf)_3$-catalyzed synthesis of tetrahydroquinoline derivatives in water through a one-pot condensation reaction of *N*-methylaniline, formaldehyde and electron-rich alkenes (Scheme 3.24).[131] The reaction was performed in commercially available aqueous formaldehyde solution, consisting of approximately 37% H_2CO and 8-10% methanol. Compared to other lanthanide triflate catalysts as well as other Lewis acids, $Dy(OTf)_3$ gave marginally better yields and was chosen for the development of the reaction. The authors were able to synthesize a variety of 1,4-disubstituted-1,2,3,4-quinolines, utilizing acyclic precursors like styrene and 1-octene, in addition to DHF.



Scheme 3.24. Scope of the dysprosium catalyzed three-component reaction in water.

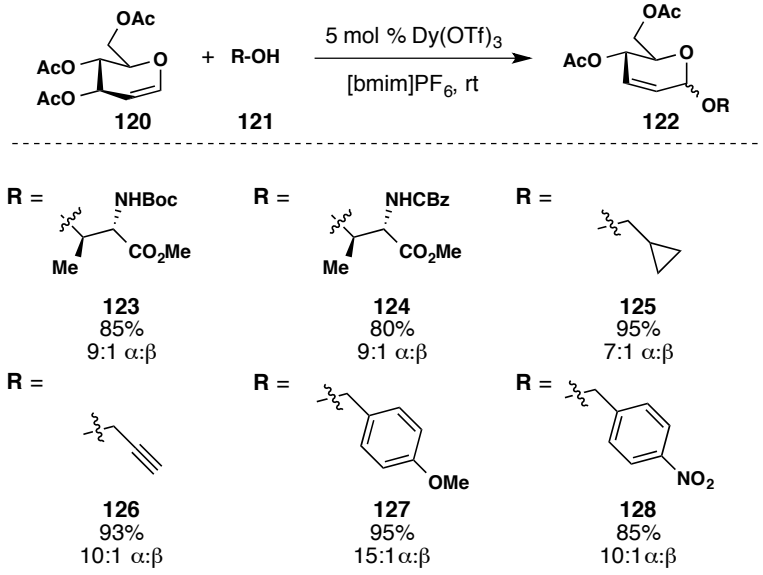
3.3.7. Dysprosium in Ionic Liquids

In the synthetic community, there is a growing interest in environmentally friendly, energy efficient reactions that will reduce the amount of waste and toxins introduced into the environment.[132] Ionic liquids are salts with a melting point below room temperature that can be employed as a green alternative to traditional solvents.[133,134] They allow for reactions to be run at room temperature in a non-volatile reaction medium that is simple to make, simple to handle and reusable.

Yadav and co-workers investigated the use of $Dy(OTf)_3$ in ionic liquids as a reusable catalyst for the synthesis of 2,3-unsaturated glycopyranosides.[135] The 2,3-unsaturated glycopyranoside motif is an important building block for the synthesis of biologically active molecules.[136] The glycosidation of glycals with alcohols was catalyzed by $Dy(OTf)_3$ in the ionic liquid 1-butyl-3-methyl-imidazolium hexafluorophosphate ([bmim]PF_6). The reaction proceeded with a variety of alcohols including 1°, 2°, phenols, allylic and propargylic

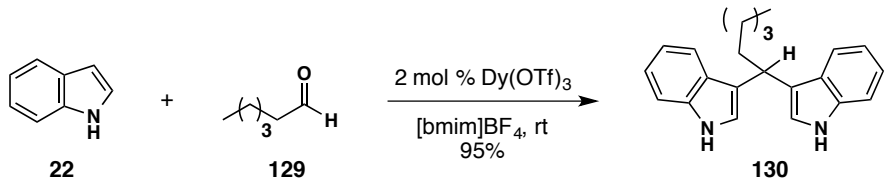
alcohols in high yields to give the α-anomer as the major glycosidation product (Scheme 3.25). The nature of the ionic liquid used in the reaction greatly affected the catalytic activity of dysprosium, where hydrophobic ionic liquids produced the highest yields. The ionic liquid and catalyst could be recycled 2 to 3 times with no effect on the yield or reaction profile.

It should be noted that at elevated temperatures and longer reaction times, the reaction proceeded without the $Dy(OTf)_3$ catalyst. Among other catalysts screened for the reaction, scandium and ytterbium performed equally well, compared to dysprosium.



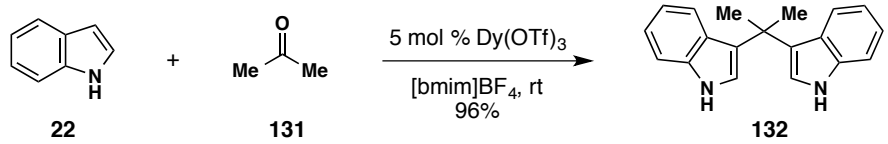
Scheme 3.25. Scope of the dysprosium catalyzed glycosidation of glycals in ionic liquid.

In another report on the use of $Dy(OTf)_3$ in ionic liquids, Cheng and co-workers detailed their development of the reaction of indoles with aldehydes and ketones.[137] To achieve suitable reaction conditions, the group initially screened a number of solvents including ionic liquids and found that 2 mol % $Dy(OTf)_3$ immobilized in $[bmim]BF_4$ afforded the desired product **130** from the reaction of indole and hexanal in 95% yield in 1 h, compared to 84% after 24 h in $EtOH/H_2O$ (2:1 v/v) with 10 mol % $Dy(OTf)_3$ (Scheme 3.26) .



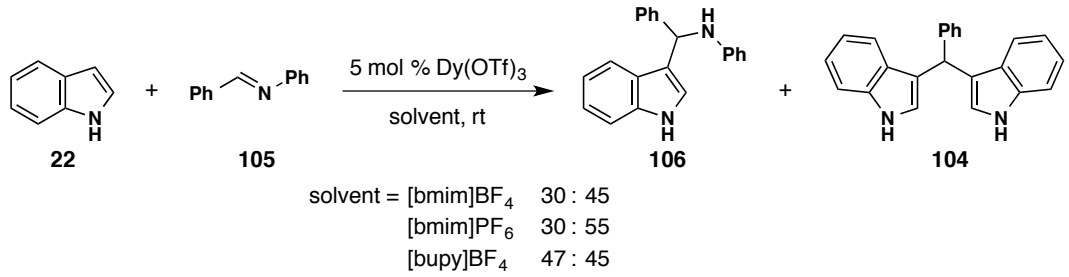
Scheme 3.26. Dysprosium catalyzed alkylation in ionic liquid.

Unlike Yadav and co-workers' glycosidation reaction,[135] Cheng's reaction of indole with aldehydes and ketones did not proceed in the absence of $Dy(OTf)_3$. Applying the reaction conditions to ketones, they found that the reaction with acetone proceeded smoothly using 5 mol % $Dy(OTf)_3$ in $[bmim]BF_4$ to afford the product **132** in 96% yield (Scheme 3.27).



Scheme 3.27. Dysprosium catalyzed alkylation of indole and acetone in ionic liquid.

Extending their reaction scope to the use of imines, Cheng and co-workers found that the reaction of indole with *N*-benzylidene aniline proceeded using 5 mol % $Dy(OTf)_3$ in $[bmim]BF_4$, giving the desired product **106** and bis(indolyl) methane **104** as a side product in a 30:45 ratio (Scheme 3.28). Switching to $[bupy]BF_4$, this ratio could be improved to 47:45 ($EtOH/H_2O$ (4:1 v/v) gave a 57:12 ratio). Importantly, similar to other work with ionic liquids, the catalyst could be recycled up to six times with no loss in reactivity. These reaction profiles in ionic liquids mimic the $Dy(OTf)_3$ catalyzed reactions in water (*vide supra*).



Scheme 3.28. Dysprosium catalyzed reaction of indole and imine in various ionic liquids.

3.4. Conclusions

Dysprosium is an extremely mild and efficient Lewis acid catalyst for numerous types of carbon–carbon bond-forming reactions. The ability of dysprosium to catalyze reactions with unprotected amines makes it a valuable catalyst for transformations in total synthesis, voiding the need for protecting groups. In addition to its mild nature, it also has a future in the development of green chemistry. Reactions can easily be performed in water and ionic liquids, and the catalyst can often be recycled without loss of activity or reactivity. The future of dysprosium chemistry will also see an increase in valuable asymmetric transformations under very mild conditions.

Our group[57,78,138–140] and Batey's[40,74] have now shown that $Dy(OTf)_3$ also makes for a great catalyst for electrocyclization reactions in the presence of amines. With that knowledge and this extensive background information on other examples of dysprosium catalysis, we are eager to see what else our group and others can accomplish with this fascinating rare earth metal catalyst.

4. The Hydroxylamine Aza-Piancatelli Rearrangement

4.1. The Value of Non-Aniline Amines

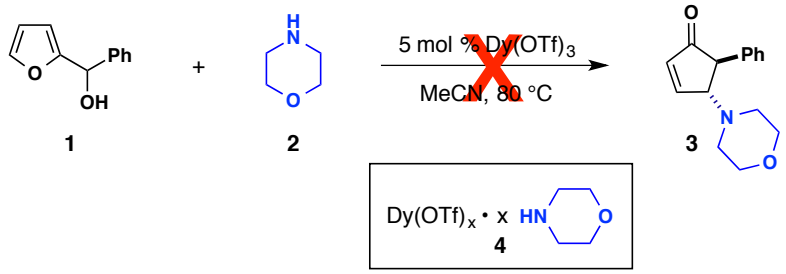
The development of the aza-Piancatelli rearrangement with anilines was a great step in the direction of a general method for the synthesis of 4-aminocyclopentenones. When examining biologically and medically relevant aminocyclopentanes however, their variety of amine functional groups makes access to non-aniline products crucial. In Chapter 2.5 we presented one solution to this problem, which employed the oxidative removal of the PMP group with periodic acid to give access to an hNK1 inhibitor. However, these reaction conditions did not translate to aminocyclopentenones that are more susceptible to decomposition under strongly oxidizing conditions. At this point we set out to find alternative amine nucleophiles for use in the aza-Piancatelli rearrangement to enable access to a larger range of 4-aminocyclopentenones.

4.2. Exploration of the Aza-Piancatelli Rearrangement with Non-Aniline Amines

We commenced our exploration of an aza-Piancatelli rearrangement with alkyl amines at the same time as the reaction with anilines, but this task proved itself infinitely more difficult to accomplish. In his development of a dysprosium catalyzed synthesis of 4,5-diamines, Batey found that the reaction worked best with secondary amines, such as morpholine, diallylamine, and *N*-methyl benzylamine (Chapter 2.2).[40] Interestingly, the reaction did not proceed with primary benzylamine and required a switch to $Sc(OTf)_3$ for the reaction with aniline.

We expected that the aza-Piancatelli rearrangement would follow a similar trend, but surprisingly we found that anilines were the best nucleophiles for our rearrangement. Reactions of furylcarbinols with secondary amines, such as morpholine or benzylamine did

not result in product formation. Instead we observed the formation of a white precipitate and complete recovery of starting material (Scheme 4.1). Presumably, the amine binds irreversibly to dysprosium to form a dysprosium-amine complex (the white precipitate (**4**)) and keeps the catalyst from activating the furylcarbinol. Various reaction conditions including increased catalyst loading, other Lewis or Brønsted acid catalysts, or addition of molecular sieves did not result in formation of the desired 4-aminocyclopentenone.



Scheme 4.1. Formation of a dysprosium-morpholine complex prevents rearrangement.

Given Batey's precedent these results were perplexing, but we surmised that the equilibrium in the aza-Piancatelli must lie too far to the left. In Batey's reaction, on the other hand, formation of aminal (**8**) pushes the equilibrium toward the 4,5-diamine forming cascade (Figure 4.1). Batey and Li observed formation of aminal **8** during NMR studies, and although it was not observed, speculated that formation of imine **6** leads to the product-forming cascade.[141] Moreover, Batey reported that imine formation occurred in the absence of a catalyst, albeit much slower. Overall, we believe that aminal formation serves two important roles that enable the use of more basic secondary amines. First, it lowers the activation barrier for ring opening of the furan by going through iminium **6**, which is the key step in the cascade rearrangement. Second, formation of the aminal (**8**) creates an off-cycle reservoir that reduces the concentration of Lewis basic nitrogen present in solution, liberating the catalyst for the desired cascade rearrangement.

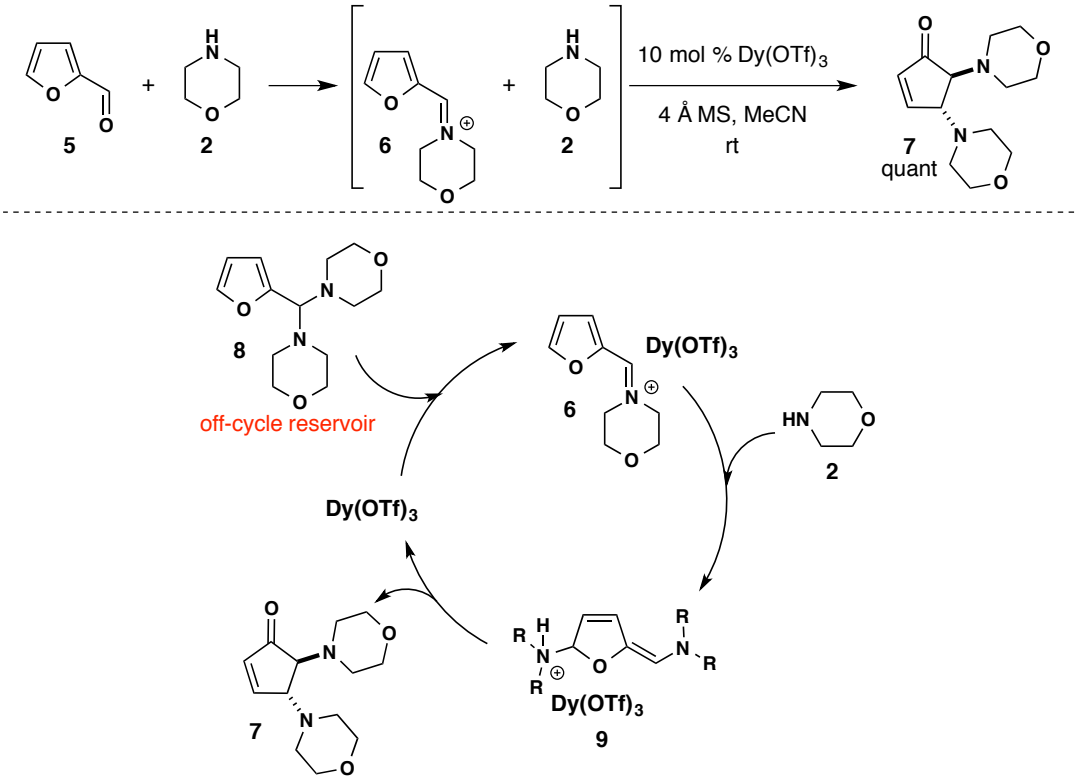
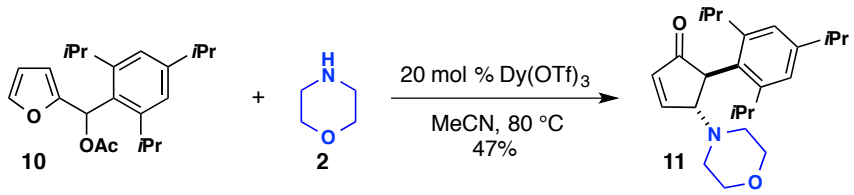


Figure 4.1. Batey's reaction proceeds from an off-cycle aminal reservoir.

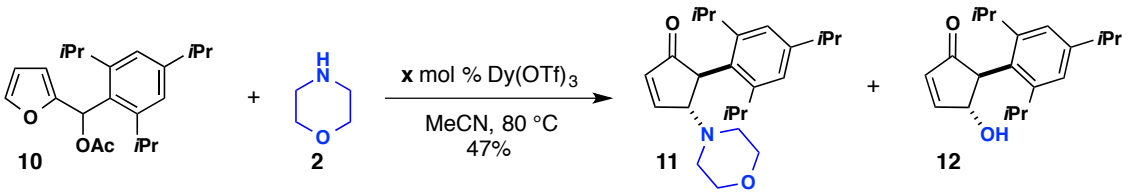
Despite initial setbacks, over the course of our studies we identified a privileged substrate, sterically hindered acylated triisopropyl furylcarbinol (**10**), that would rearrange with morpholine (**2**) when treated with 20 mol % $Dy(OTf)_3$ to give the desired 4-morpholino-cyclopentenone (**11**) in a respectable 47% yield (Scheme 4.2). We believe that the unusual reactivity of **10** can be attributed to both the increased activation from the acyl group, as well as steric hindrance from the isopropyl groups, which blocks products derived from substitution and directs the reaction to the productive rearrangement.



Scheme 4.2. Aza-Piancatelli rearrangement with morpholine.

Unfortunately, we were unable to improve the reaction yield and the water product from a Piancatelli rearrangement (**12**) was a common side product. In fact, our investigations showed that increasing the catalyst loading led to increased formation of the Piancatelli product **12** (Table 4.1), suggesting water outcompetes the amine nucleophile. This is the first time that this competitive reactivity was observed.

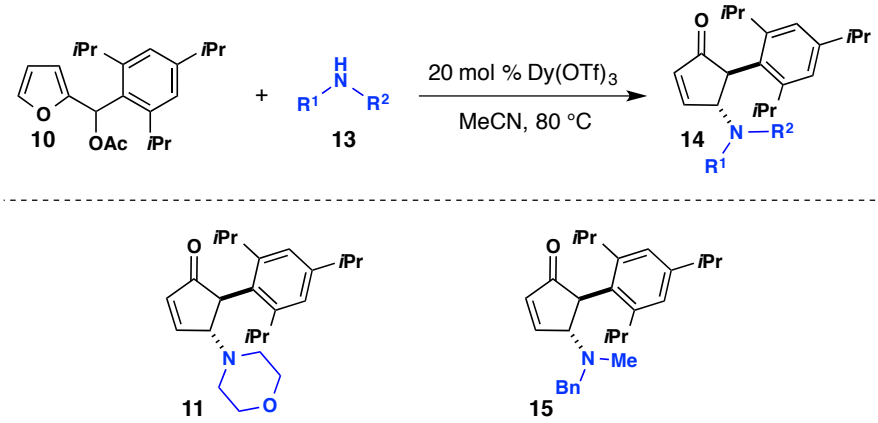
Table 4.1. Effect of catalyst loading on product formation.



Entry	x	Product ratio (11:12)
1	30	1:0.4
2	40	1:0.8
3	50	0.7:1.0
4	70	0.3:1.0
5	90	0.1:1

Although several other amines participated in the rearrangement with this privileged furylcarbinol (Table 4.2), these reactions proceeded extremely slowly, taking several days, and often did not go to completion.

Table 4.2. Selected scope of the rearrangement with privileged furylcarbinol **10**.



We eventually surmised that the electronic nature of the amine plays a more significant role in the success of the reaction than activating the furylcarbinol. Operating under the assumption that the pKa of the amine is key to a successful aza-Piancatelli rearrangement, we explored the reaction with a range of amines from basic morpholine (pKa = 8.4 to more acidic *N*-methylacetamide (pKa = –0.5). As a general rule, anilines and other amines with a pKa around 4.7 readily participate in the rearrangement, while amines with a higher pKa bind irreversibly to dysprosium and shut down the reaction. Amines with a lower pKa than anilines are neither basic enough to bind to dysprosium nor nucleophilic enough to attack at the 5-position of furylcarbinol resulting in complete decomposition of furylcarbinol (Figure 4.2).

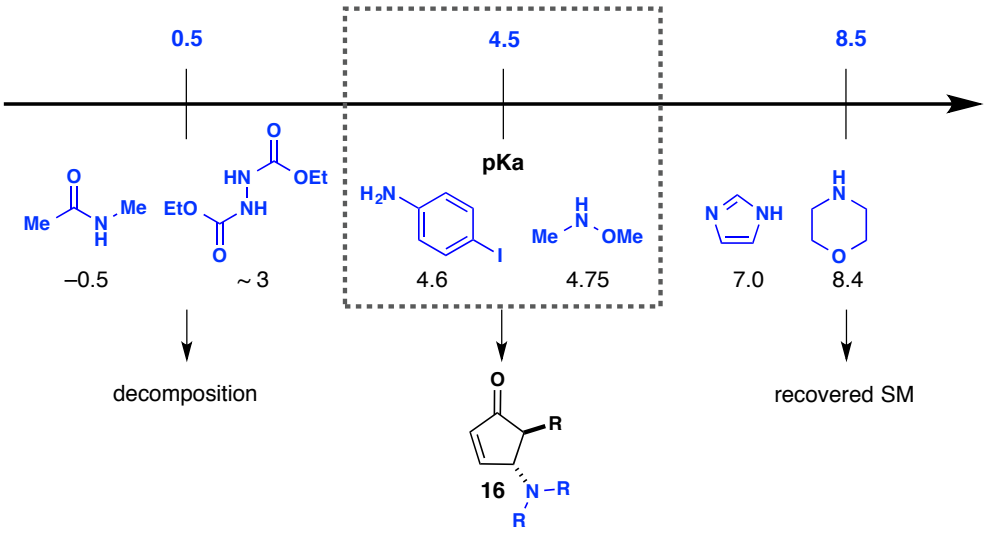
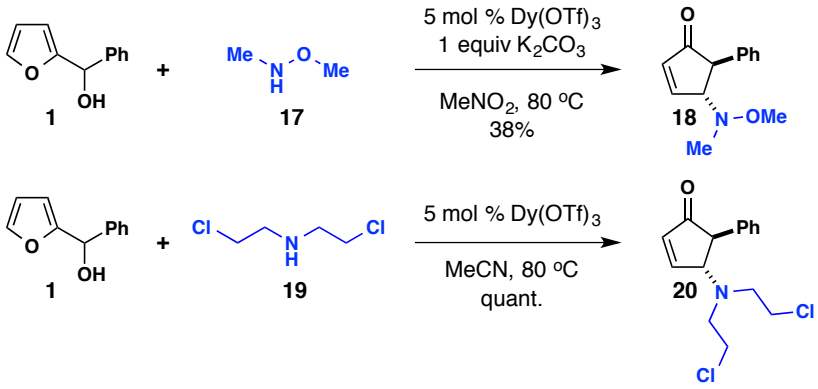


Figure 4.2. Reaction outcome with varying amine pKa value.

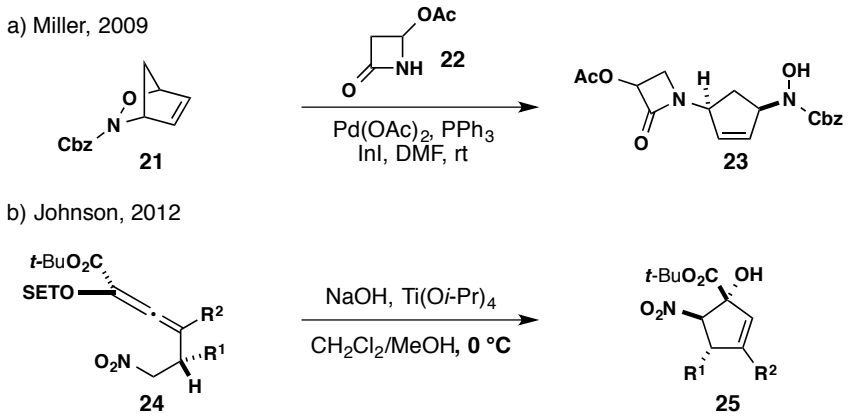
Exploring amines with pKa values similar to aniline, we were pleased to find that *N*-methyl-*O*-methyl hydroxylamine (**17**) and bis(2-chloroethyl)amine (**19**) proved viable nucleophiles for the aza-Piancatelli rearrangement (Scheme 4.3).[142]



Scheme 4.3. Successful rearrangement with *N*-methyl-*O*-methyl hydroxylamine and bis(2-chloroethyl)amine.

Due to some concerns about the potential formation of nitrogen mustards[143] from bis(2-chloroethyl)amine and limited success with other electronically similar amines, we chose to focus on developing the reaction with hydroxylamines. We became particularly excited about hydroxylamines as a new class of nucleophiles for the aza-Piancatelli rearrangement because the intrinsically weak nitrogen–oxygen bond (55 kcal/mol) of hydroxylamines is easily cleaved to reveal the alkylamine.[144–147]

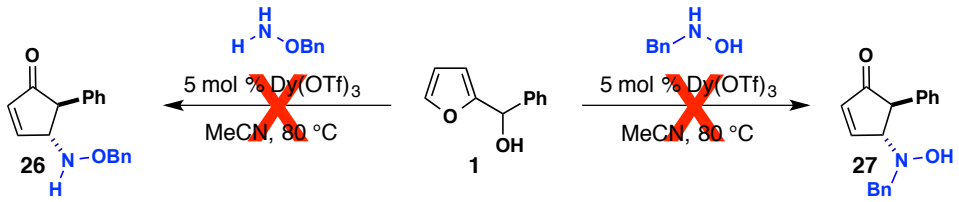
Additionally, there is not much work in the area of substituted cyclopentanes with N–O bonds despite their potential synthetic utility. Miller's work is limited to HDA reactions with cyclopentadiene and derivatives,[62] while Johnson's work enables access to NO_2-substituted cyclopentanes (Scheme 4.4).[66]



Scheme 4.4. Synthesis of aminocyclopentanes by Miller and Johnson.

4.3. Development of a Hydroxylamine Aza-Piancatelli Rearrangement

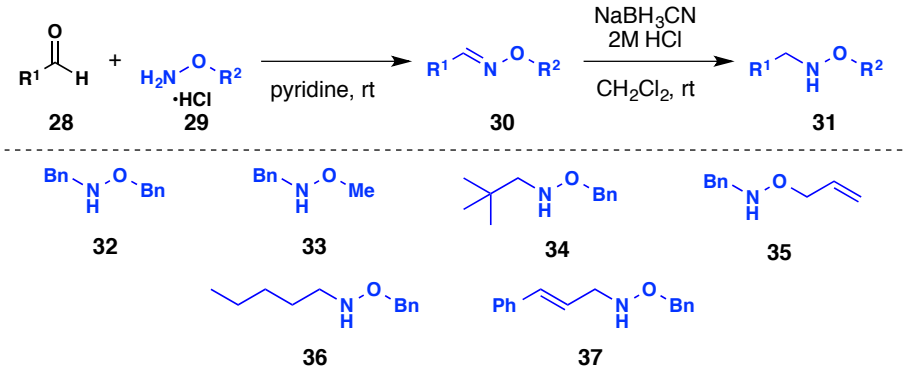
With the encouraging result from the reaction of *N*-methyl-*O*-methyl hydroxylamine with phenyl furylcarbinol in hand (Scheme 4.3a), we set out to evaluate the scope of a hydroxylamine aza-Piancatelli rearrangement. Initial investigations with commercially available *N*-benzylhydroxylamine and *O*-benzylhydroxylamine disappointingly resulted in no reaction (Scheme 4.5).



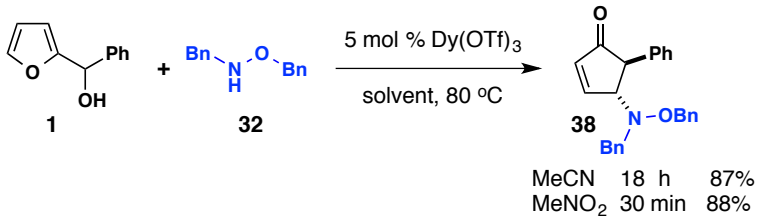
Scheme 4.5. First attempts at a hydroxylamine aza-Piancatelli rearrangement.

Speculating that the free hydroxyl group or amine might bind too strongly to dysprosium or compete as a nucleophile, we decided to evaluate *N*,*O*-disubstituted hydroxylamines. Importantly, these adducts can be accessed by simple condensation of the *O*-alkyl hydroxylamine with an aldehyde, followed by reduction with $NaBH_3CN$ affords the desired secondary amine nucleophile (Table 4.3).[144,148–150]

Table 4.3. General method for the synthesis of disubstituted hydroxylamines.

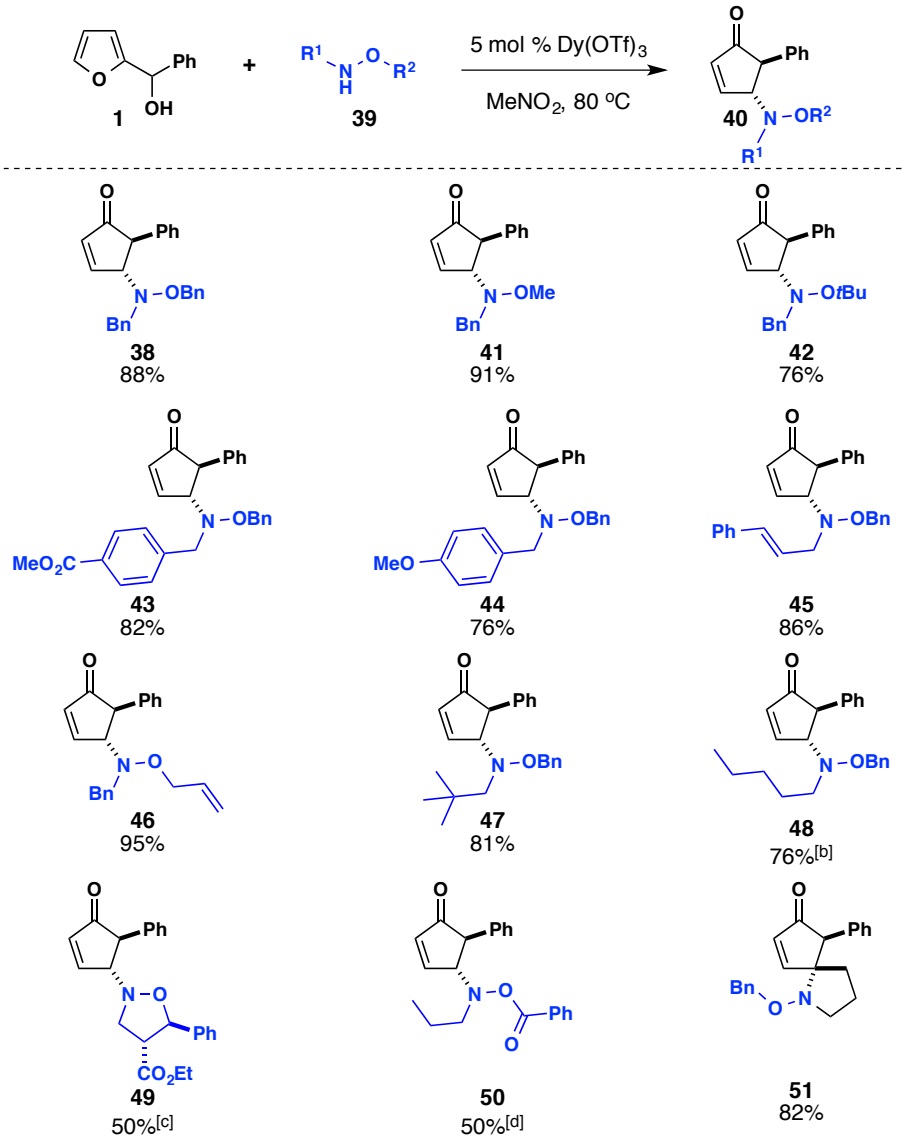


We were pleased to find that the reaction of phenyl furylcarbinol (**1**) and *N*-benzyl-*O*-benzyl hydroxylamine (**32**) proceeded cleanly under the reaction conditions developed for the aza-Piancatelli rearrangement (5 mol % $Dy(OTf)_3$, MeCN, 80 °C) to give *trans*-substituted 4-hydroxyalmine-substituted cyclopentenone **38** in 87% yield (Scheme 4.6). A quick screen of reaction conditions revealed nitromethane ($MeNO_2$) as a superior solvent, reducing the reaction time from 18 h to 30 min (Scheme 4.6).



Scheme 4.6. Development of reaction conditions for the hydroxylamine aza-Piancatelli rearrangement.

Table 4.4. Scope of the hydroxylamine aza-Piancatelli rearrangement with **1**.[a]



[a] Isolated yields. [b] The reaction was performed with 10 mol % $Dy(OTf)_3$. [c] Isolated as a 1:1 mixture of *trans* diastereomers. [d] The reaction was performed with 30 mol % $Dy(OTf)_3$.

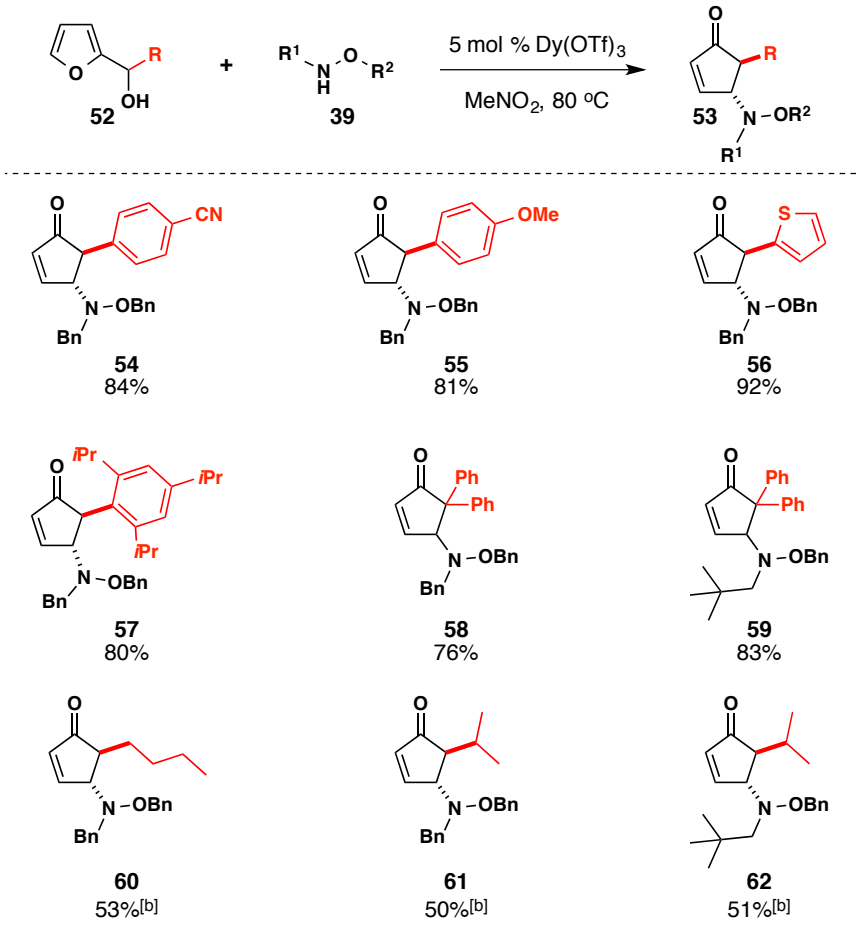
With the optimized reaction conditions in hand, we set out to develop the scope of the transformation. Gratifyingly, the rearrangement of furylcarbinols proceeded with a wide range of substituted hydroxylamines, as summarized in Table 4.4. A variety of alkyl substituents at the *O*-terminus were tolerated including benzyl, methyl, bulky *t*-butyl and allyl (Table 4.4, **38**, **41**, **42**, **46**, respectively).

The benzyl substituent at the *N*-terminus could be modified with electron donating or withdrawing groups with only a small effect on the yield of the reaction (Table 4.4, **44** and **43**). Cinnamaldehyde- and the bulky pivalaldehyde-derived hydroxylamines participated in the rearrangement to give the desired products **45** and **47** in good yield.

Moving to an extended alkyl chain hydroxylamine, we found that an increase in catalyst loading to 10 mol % $Dy(OTf)_3$ was required to generate the desired product at a sufficient rate (Table 4.4, **48**). Pleasingly, a cyclic hydroxylamine and O-benzoyl hydroxylamine also participated in the rearrangement to give cyclopentenone **49** and **50** in acceptable 50% yield. Finally, we demonstrated that phenyl furylcarbinol with a pendent hydroxylamine readily rearranged in an intramolecular fashion to give spirocyclic **51** in 82% yield.

To get a more complete picture of the hydroxylamine aza-Piancatelli rearrangement, we also explored the scope of furylcarbinols that will participate in the rearrangement, summarized in Table 4.5. Similar to the aza-Piancatelli rearrangement with anilines, the electron donating *p*-methoxy group increases the rate of the reaction (Table 4.5, **55**), while an electron withdrawing *p*-nitrile group has the opposite effect on the rate of the reaction (Table 4.5, **54**). Thiophene-substituted furylcarbinol rearranged cleanly to give **56** in 92% yield, again highlighting the difference between the ability of furan and thiophene to participate in dearomatizing reactions (*vide supra*). Privileged triisopropylphenyl furylcarbinol reacted with *N*-benzyl-*O*-benzyl hydroxylamine to give **57**, and tertiary bis-phenyl furylcarbinol reacted with *N*-benzyl-*O*-benzyl hydroxylamine or *N*-benzyl-*O*-neopentyl hydroxylamine to give quaternary stereocenter-featuring **58** and **59**, respectively (Table 4.5).[140]

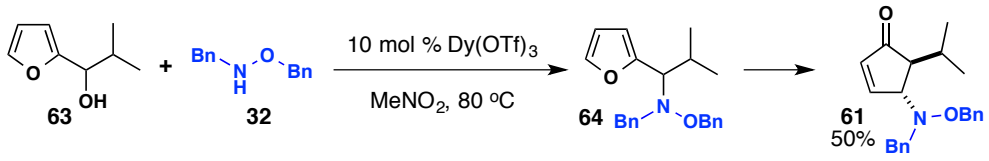
Table 4.5. Scope of furylcarbinols in the hydroxylamine aza-Piancatelli rearrangement.



[a] Isolated yields. [b] The reaction was performed with 10 mol % $Dy(OTf)_3$.

Exploring alkyl-substituted furylcarbinols proved to be more challenging with hydroxylamines (Table 4.5, **60-62**). When reactions with these substrates were performed in MeCN, only decomposition was observed. Upon monitoring the reaction of isopropyl furylcarbinol with *N*-benzyl-*O*-benzyl hydroxylamine closely by TLC, we made two observations. For one, we observed the formation of a more non-polar species, corresponding to the substitution product, **64** (Scheme 4.7). It should be noted that substitution products were observed in almost all cases of the hydroxylamine aza-Piancatelli rearrangement, in contrast to the aniline reaction where they were only observable in certain

cases. The formation of the substitution product in mechanistically interesting but it does not affect the overall outcome of the reaction because it is an intermediate that can re-enter the catalytic cycle (Figure 4.3, **66** to **65**). In addition to the formation of substitution product **64**, the appearance of compound with the expected R_f of cyclopentenone **61** was observed, but this species quickly disappeared, and no desired product was isolated from the reaction. It was gratifying to find that when switching to $MeNO_2$, **61** could be isolated in 50% yield when using 10 mol % $Dy(OTf)_3$. Using these conditions, 5-alkyl substituted cyclopentenones **60** and **62** could also be formed in moderate yield (Table 4.5).



Scheme 4.7. Formation of alkyl-substituted cyclopentenones via the substitution product.

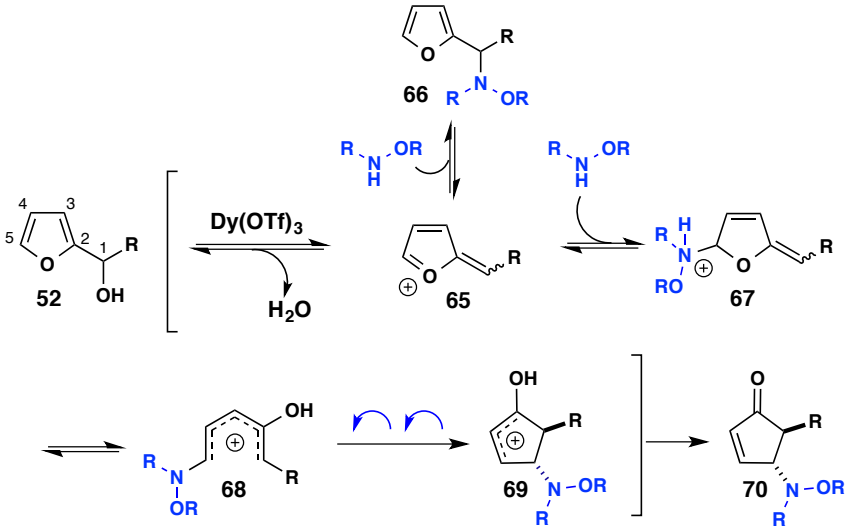


Figure 4.3. Proposed mechanism showing the off-cycle substitution event in the hydroxylamine aza-Piancatelli rearrangement.

With the scope of the hydroxylamine aza-Piancatelli rearrangement fully developed, we were ready to explore the potential of these densely functionalized small molecules and the possibility of accessing alkylamines via N–O bond cleavage.

4.4. Functionalization of Hydroxylamine-Substituted Cyclopentenones

Close examination of the 4-aminocyclopentenones produced in the hydroxylamine aza-Piancatelli rearrangement reveals the potential for structural modification at several points of the molecule (Figure 4.4). To rationally highlight this potential we investigated a range of reactions at each site marked with a green arrow.

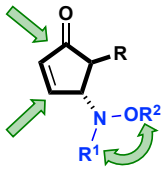
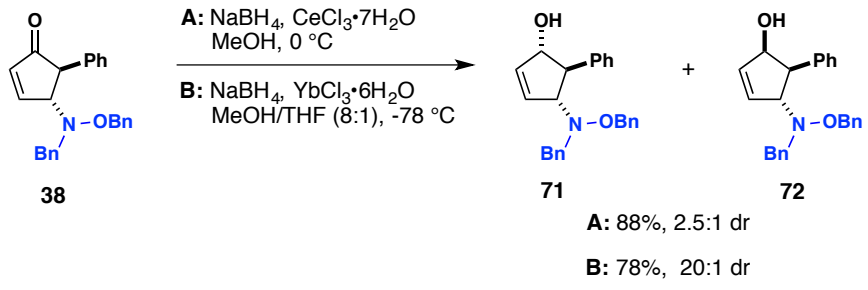


Figure 4.4. Points of functionalization around the 4-aminocyclopentenone core.

A Luche reduction of the enone facilitated access to the 1,2-*trans*-2,3-*trans* substituted cyclopentene core, reminiscent of our previously synthesized hNK1 inhibitor. Standard Luche reduction with cerium chloride at 0 °C resulted in 2.5:1 diastereomeric ratio (dr) of allylic alcohol **71**:**72**, similar to our previous results (Scheme 4.8, conditions **A**). Interestingly, a simple switch to ytterbium chloride hexahydrate ($YbCl_3$•$6H_2O$) and lowering the reaction temperature to –78 °C resulted in up to 20:1 dr (Scheme 4.8, conditions **B**). This represents a huge improvement in selectivity, and I am confident that this improvement would apply to the hNK1 inhibitor synthesis. The stereochemistry of the major product (**71**) was confirmed to possess a 1,2-*trans*-2,3-*trans* relationship by single crystal X-Ray diffraction (Figure 4.5).



Scheme 4.8. Results of Luche-type reductions of the cyclopentenone.

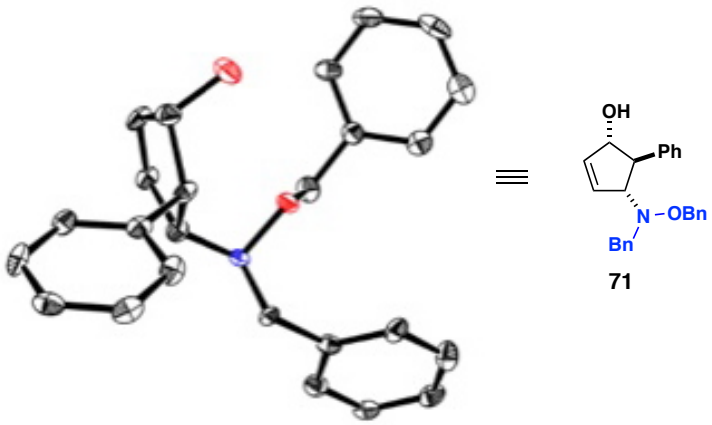
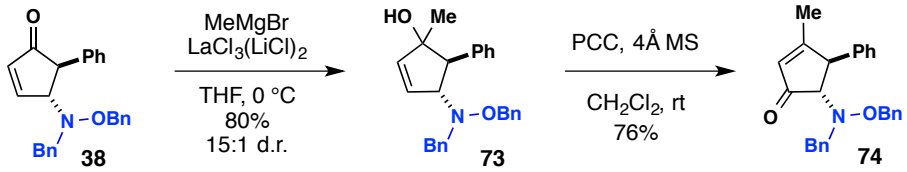


Figure 4.5. ORTEP drawing of the crystal structure of the major diastereomer of the Luche reduction with 50% thermal ellipsoids. CCDC 986010.

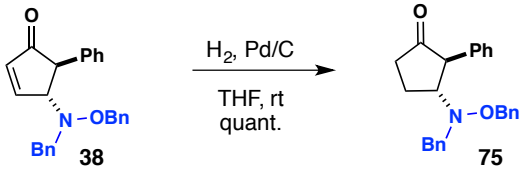
Continuing modification of the ketone, we explored 1,2-addition at this position. Addition of *n*-butyllithium was unsuccessful, and Grignard reaction was not selective for the desired 1,2-addition. However, addition of methylmagnesium bromide using Knochel's conditions provided **73** in 80% yield and 15:1 dr (Scheme 4.9).[151] With this tertiary allylic alcohol in hand, we were excited to attempt an allylic transposition. To our delight, treatment with pyridinium chlorochromate (PCC) resulted in clean formation of **74** (Scheme 4.9).[152] This is an exciting prospect since the aza-Piancatelli coupled with this allylic transposition now provides access to both 4-aminocyclopentenones (**38**) and 2-

aminocyclopentenones (**74**). Additionally, the *trans*-relationship established during the 4π electrocyclization is conserved.



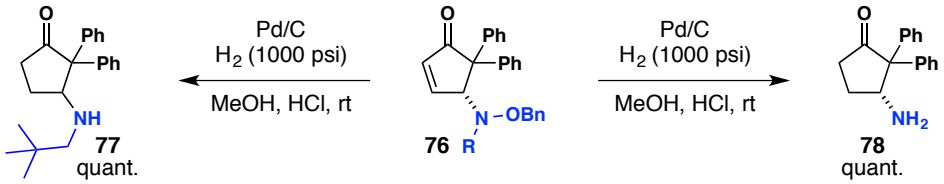
Scheme 4.9. Selective 1,2-Grignard addition followed by allylic transposition.

Finally, as mentioned above, we were enthusiastic about the prospect of the hydroxylamine aza-Piancatelli rearrangement because cleavage of the weak N–O bond generates access to valuable alkylamines. Unfortunately, despite ample literature precedent for the cleavage of N–O bonds, this step proved much more difficult than anticipated. Treatment of cyclopentenone **38** with hydrogenation over palladium on carbon resulted in reduction of the alkene, providing cyclopentanone **75** in quantitative yield, but no N–O bond cleavage (Scheme 4.10). No reaction or decomposition was observed when using SmI_2,[144] $Mo(CO)_6$,[146] or even Zn/HCl.[147]



Scheme 4.10. Hydrogenation of a hydroxylamine cyclopentenone.

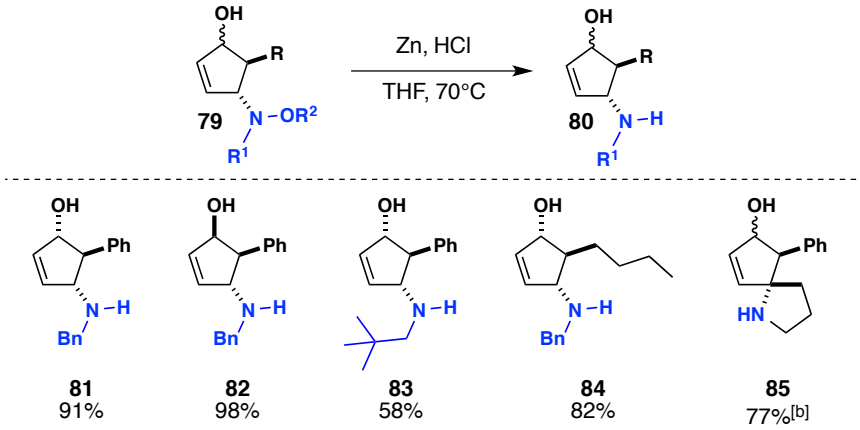
Speculating that the acidic proton alpha to the carbonyl might be the source of our difficulties, we examined **58** and **59** with quaternary stereocenters. Gratifyingly, hydrogenation of these substrates proceeded cleanly to give primary amine **78** or secondary alkyl amine **77** in quantitative yield (Scheme 4.11).[145]



Scheme 4.11. Successful N–O bond cleavage of diphenyl-substituted cyclopentenones.

With the knowledge that the N–O bond could in fact be clipped, and that the acidic alpha proton might be the source of our difficulties, we chose to examine bond cleavage from the allylic alcohol. Our speculations proved valid, and we found that treatment of a variety of allylic alcohols with Zn/HCl resulted in formation of the desired alkyl amines (Table 4.6). The reaction proceeded with either the major 1,2-*trans* or *1,2*-cis isomer (**71** or **72**), and the nature of the R group can be either aryl (**81**) or alkyl (**84**). We were most excited about the result with aza-spirocyclic substrate **85**, since this may enable entry to the total synthesis of homoharringtonine (**87**) and stemonamine (**88**) from the same spirocyclic precursor (**86**) (Figure 4.6).

Table 4.6. Scope of the N–O bond cleavage from the allylic alcohol.



[a] Isolated yields. [b] The starting material came from an 8:1 mixture of diastereomers.

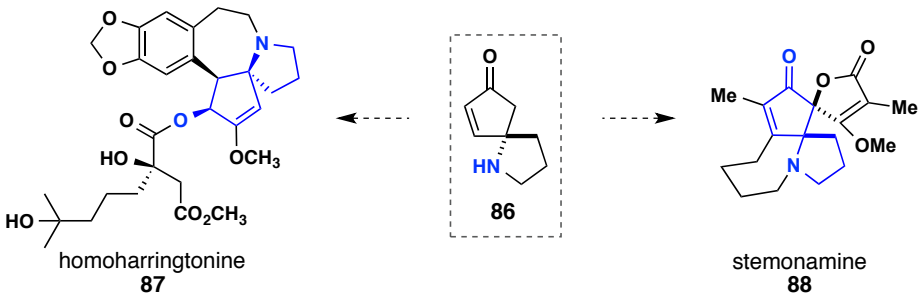
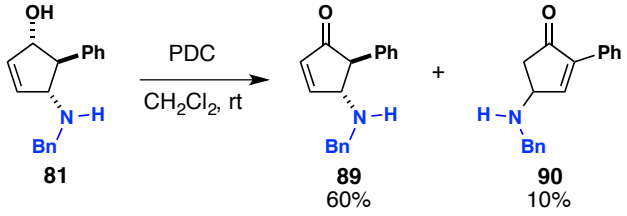


Figure 4.6. Potential intermediate for the synthesis of homoharringtonine and stemonamine.

Finally, we were happy to find that pyridinium dichromate (PDC) in CH_2Cl_2 enabled the oxidation of **81** to the desired cyclopentenone **89** in 60% yield (Scheme 4.12). It should be noted that in this case, 10% of the rearranged cyclopentenone **90** was also isolated. The desired product may also rearrange upon extended time on the benchtop at rt, or if the complete work-up procedure is not completed immediately upon completion of the reaction.



Scheme 4.12. Oxidation to the desired aminocyclopentenone.

4.5. Summary

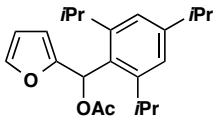
In conclusion, we developed a new method to access hydroxylamine-substituted cyclopentenones in a single step from furfural derived precursors. We showed that this scaffold could further be manipulated with a variety of transformations. Most importantly, we were able to cleave the N–O bond to access alkylamines. Even though this transformation adds several steps to the synthesis, it marks great progress from the aniline aza-Piancatelli rearrangement. These studies are helping us to truly understand the

transformation from a synthetic standpoint, but a deeper mechanistic and fundamental understanding is still needed.

4.6. Experimental Procedures

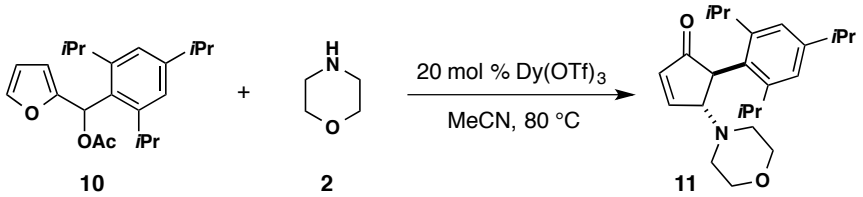
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using an Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 0.040 – 0.063 mm, Geduran). ^{1}H NMR spectra were recorded on Varian spectrometers (at 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 or 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum 100 FT/IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source. X-ray data were obtained from the UC Santa Barbara X-ray Facility.

Reactions with a privileged furylcarbinol



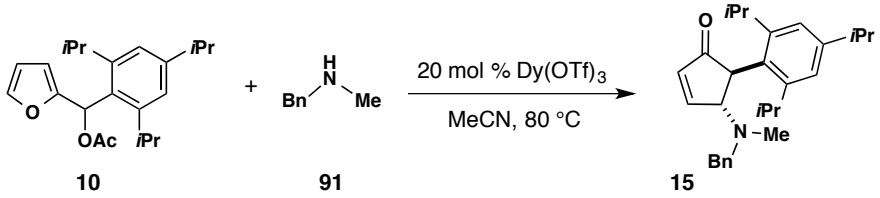
10

Furan-2-yl(2,4,6-triisopropylphenyl)methyl acetate (10): Brown solid; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.39 (dd, *J* = 1.0, 1.1 Hz, 1H), 7.05 (s, 2H), 6.29 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.98 (ddd, *J* = 3.3, 1.1, 1.1 Hz, 1H), 3.39 (dt, *J* = 6.8, 6.8 Hz, 2H), 2.89 (dt, *J* = 7.0, 7.0 Hz, 1H), 2.13 (s, 3H), 1.26 (dd, *J* = 7.0, 1.4 Hz, 6H), 1.24 – 1.17 (m, 6H), 1.15 (d, *J* = 6.8 Hz, 6H) ppm.



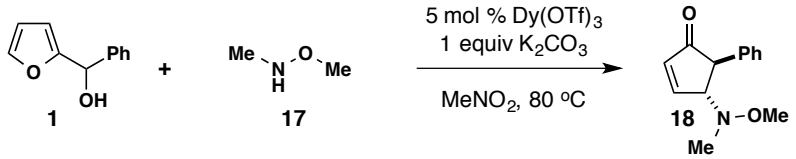
10 2 11

4-Morpholino-5-(2,4,6-triisopropylphenyl)cyclopent-2-en-1-one (11): Brown oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.45 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.01 (d, *J* = 3.4 Hz, 1H), 3.98 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.69 (dd, *J* = 4.6, 4.6 Hz, 4H), 3.21 (hept, *J* = 6.7 Hz, 1H), 2.86 (hept, *J* = 6.8 Hz, 1H), 2.69 (ddd, *J* = 11.3, 4.6, 4.6 Hz, 2H), 2.54 (ddd, *J* = 11.4, 4.6, 4.6 Hz, 2H), 2.09 – 1.99 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 7.0 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H) ppm.



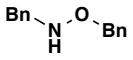
10 91 15

4-(Benzyl(methyl)amino)-5-(2,4,6-triisopropylphenyl)cyclopent-2-en-1-one (15): Brown oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 6.0, 1.8 Hz, 1H), 6.99 (d, *J* = 1.9 Hz, 1H), 6.95 (d, *J* = 1.9 Hz, 1H), 6.45 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.01 (d, *J* = 3.4 Hz, 1H), 3.98 (dd, *J* = 3.6, 1.8 Hz, 1H), 3.69 (dd, *J* = 4.6, 4.6 Hz, 4H), 3.21 (dt, *J* = 6.9, 6.9 Hz, 1H), 2.86 (dt, *J* = 6.9, 6.8 Hz, 1H), 2.69 (ddd, *J* = 11.4, 4.6, 4.6 Hz, 2H), 2.54 (ddd, *J* = 11.3, 4.6, 4.6 Hz, 2H), 2.08 – 1.98 (m, 1H), 1.36 (d, *J* = 6.7 Hz, 3H), 1.24 (d, *J* = 6.9 Hz, 6H), 1.22 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H) ppm.



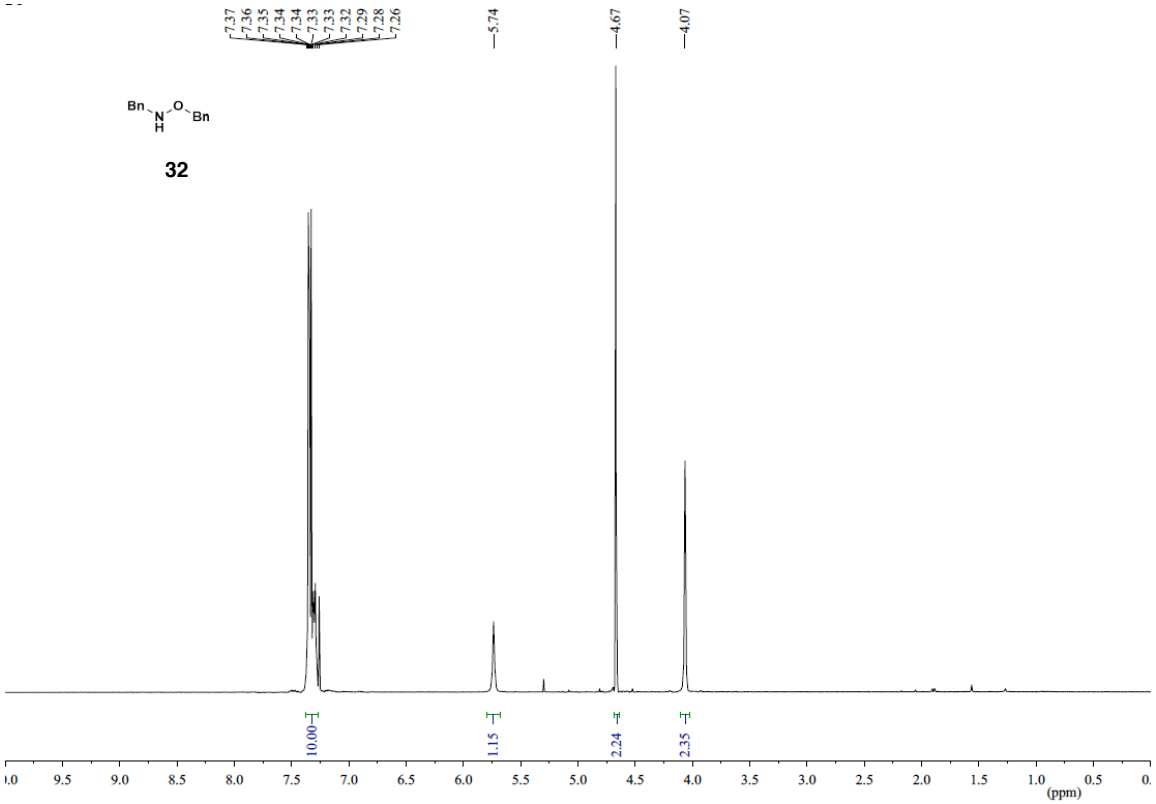
4-(Methoxy(methyl)amino)-5-phenylcyclopent-2-en-1-one (18): Brown oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.28 – 7.23 (m, 1H), 7.16 – 7.11 (m, 2H), 6.40 (dd, *J* = 5.9, 1.8 Hz, 1H), 4.10 (dd, *J* = 2.3, 2.3 Hz, 1H), 3.64 (s, 1H), 3.51 (s, 3H), 2.63 (s, 3H) ppm.

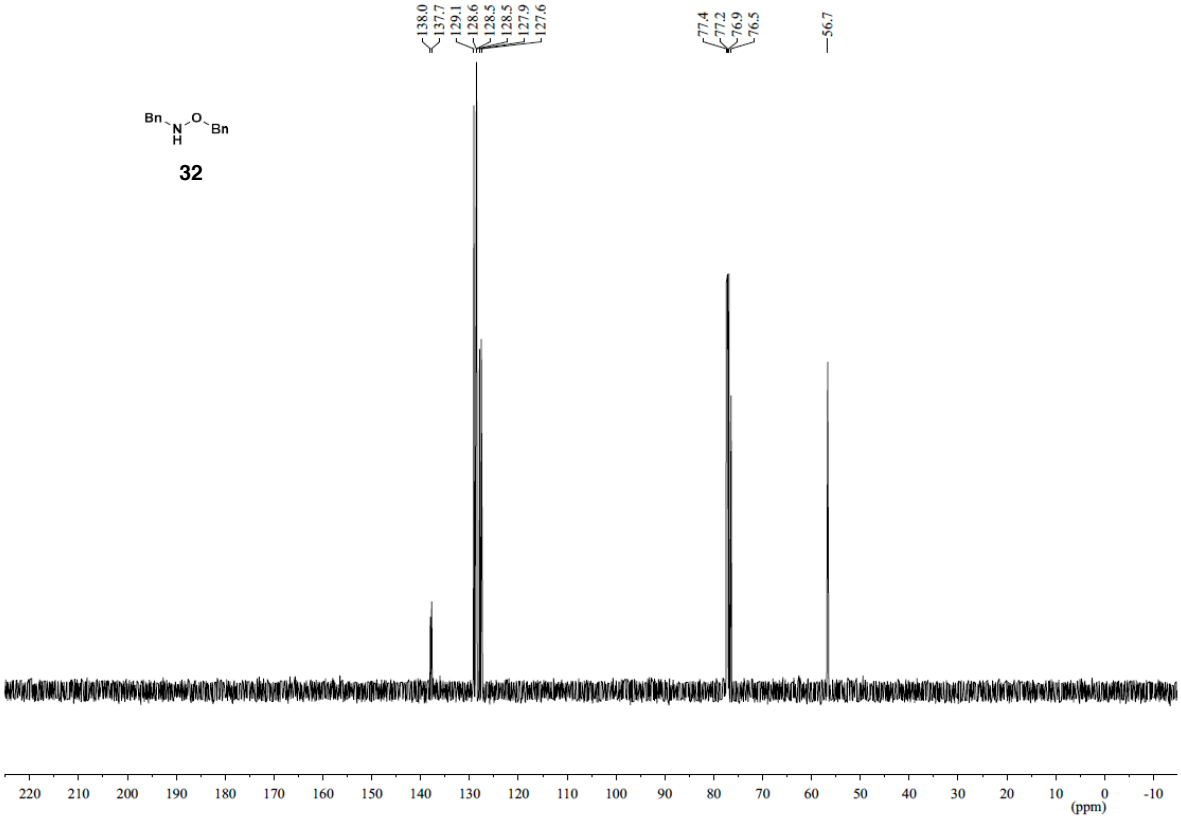
General Procedure for the Synthesis of Hydroxylamines: Hydroxylamines were synthesized following published procedures.[144,149,150]

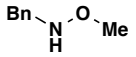


32

***N*,*O*-Dibenzylhydroxylamine (32):** Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 10H), 5.74 (s, 1H), 4.67 (s, 2H), 4.07 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.0, 137.7, 129.1, 128.6, 128.5, 128.5, 127.9, 127.6, 76.5, 56.7 ppm; **IR** (thin film) 3260, 3087, 3019, 2912, 2858, 1895, 1877, 1810, 1604, 1495, 1453, 1275, 1260, 988 cm^{-1}; **MS** (ESI) *m/z* 214.1219 (214.1232 calcd for $C_{14}H_{16}NO^+$ $[MH]^+$).

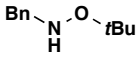

7.37
7.36
7.35
7.34
7.34
7.34
7.33
7.33
7.32
7.29
7.28
7.26
5.74
4.67
4.07
Bn
N
H
O
Bn
32
10.00
1.15
2.24
2.35
(ppm)


138.0
137.7
129.1
128.6
128.5
128.5
127.9
127.6
77.4
77.2
76.9
76.5
56.7
Bn
N
H
O
Bn
32
(ppm)



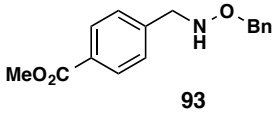
33

***N*-Benzyl-*O*-methylhydroxylamine (33):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.32 (m, 4H), 7.31 – 7.27 (m, 1H), 5.73 (s, 1H), 4.06 (s, 2H), 3.52 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.7, 129.0, 128.6, 127.6, 62.0, 56.4 ppm; **IR** (thin film) 3259, 3030, 2937, 2894, 2808, 1604, 1454, 1275, 1260, 992 cm^{-1}; **MS** (ESI) *m/z* 160.0737 (160.0738 calcd for $C_8H_{11}NNaO^+$ $[MNa]^+$).



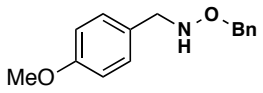
92

***N*-Benzyl-*O*-(tert-butyl)hydroxylamine (92):** Colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.27 (m, 5H), 4.00 (s, 2H), 1.18 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 129.4, 128.5, 127.6, 57.8, 26.9 ppm; **IR** (thin film) 3255, 2975, 2929, 2863, 1947, 1876, 1806, 1603, 1454, 1360 cm^{-1}; **MS** (ESI) *m/z* 180.1362 (180.1383 calcd for $C_{11}H_{18}NO^+$ $[MH]^+$).



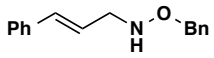
93

Methyl 4-(((benzyloxy)amino)methyl)benzoate (93): Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.38 – 7.27 (m, 5H), 4.63 (s, 2H), 4.09 (s, 2H), 3.92 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.1, 143.3, 137.8, 129.8, 129.4, 128.9, 128.6, 128.5, 128.0, 76.6, 56.3, 52.2 ppm; **IR** (thin film) 3267, 3031, 2951, 1937, 1721, 1612 cm^{-1}; **MS** (ESI) *m/z* 294.1096 (294.1106 calcd for $C_{16}H_{17}NNaO_3^+$ $[MNa]^+$).



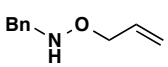
94

***O*-Benzyl-*N*-(4-methoxybenzyl)hydroxylamine (94):** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.37 (d, *J* = 3.0 Hz, 4H), 7.35 – 7.32 (m, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.6 Hz, 2H), 5.68 (bs, 1H) 4.70 (s, 2H), 4.03 (s, 2H), 3.83 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 159.1, 138.0, 130.3, 129.7, 128.5, 128.4, 127.8, 113.9, 76.3, 56.0, 55.3 ppm; **IR** (thin film) 3261, 3031, 2910, 2859, 2060, 1883, 1612, 1513 cm^{-1}; **MS** (ESI) *m/z* 244.1319 (244.1332 calcd for $C_{15}H_{18}NO_2^+$ $[MH]^+$).



37

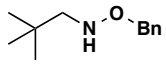
***O*-Benzyl-*N*-cinnamylhydroxylamine (37):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 9H), 7.27 – 7.21 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.6 Hz, 1H), 5.61 (s, 1H), 4.76 (s, 2H), 3.72 (dd, *J* = 6.6, 1.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.0, 137.1, 133.3, 128.7, 128.6, 128.5, 128.0, 127.7, 126.5, 125.7, 76.5, 54.6 ppm; **IR** (thin film) 3258, 3061, 3028, 2910, 2853, 1877, 1598, 1494, 1453, 1361, 1275, 1260, 965^{-1}; **MS** (ESI) *m/z* 240.1381 (240.1388 calcd for $C_{16}H_{18}NO^+$ $[MH]^+$).



35

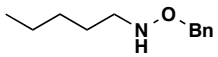
***O*-Allyl-*N*-benzylhydroxylamine (35):** Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.30 (m, 4H), 7.32 – 7.25 (m, 1H), 5.91 (ddt, *J* = 17.3, 10.4, 5.9 Hz, 1H), 5.72 (s, 1H), 5.26 (ddt, *J* = 17.3, 1.6, 1.6 Hz, 1H), 5.18 (ddt, *J* = 10.4, 2.0, 1.2 Hz, 1H), 4.17 (ddd, *J* = 6.0,

1.3, 1.3 Hz, 2H), 4.07 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.6, 134.6, 129.1, 128.5, 127.6, 117.7, 75.2, 56.7 ppm; **IR** (thin film) 3254, 3065, 3030, 2907, 2858, 1807, 1645, 1454, 1421, 1343, 1239, 988, 923 cm^{-1}; **MS** (ESI) *m/z* 186.0873 (186.0895 calcd for $C_{10}H_{13}NNaO^+$ $[MNa]^+$).



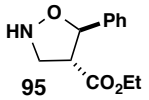
34

***O*-Benzyl-*N*-neopentylhydroxylamine (34):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.38 – 7.33 (m, 4H), 7.32 – 7.28 (m, 1H), 5.60 (s, 1H), 4.70 (s, 2H), 2.75 (s, 2H), 0.93 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.1, 128.6, 128.4, 127.8, 75.9, 63.6, 31.1, 28.3 ppm; **IR** (thin film) 3276, 3031, 2953, 2906, 2865, 1476, 1454, 1363, 1275, 1259, 978 cm^{-1}; **MS** (ESI) *m/z* 194.1523 (194.1545 calcd for $C_{12}H_{20}NO^+$ $[MH]^+$).



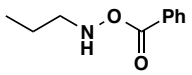
36

***O*-Benzyl-*N*-pentylhydroxylamine (36):** Colorless oil; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 4H), 7.32 – 7.27 (m, 1H), 5.54 (s, 1H), 4.71 (s, 2H), 2.93 (dd, *J* = 7.3, 7.3 Hz, 2H), 1.52 (dddd, *J* = 7.4, 7.4, 7.4, 7.4 Hz, 2H), 1.36 – 1.25 (m, 4H), 0.90 (dd, *J* = 6.8, 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 128.5, 128.5, 127.9, 76.3, 52.4, 29.5, 27.2, 22.7, 14.2 ppm; **IR** (thin film) 3265, 3031, 2955, 2930, 1857, 1454, 1362, 1275, 1206, 998 cm^{-1}; **MS** (ESI) *m/z* 194.1535 (194.1545 calcd for $C_{12}H_{20}NO^+$ $[MH]^+$).



95

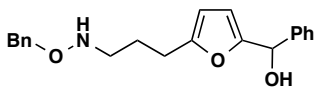
Ethyl (*trans*)-5-phenylisoxazolidine-4-carboxylate (95): Prepared according to literature procedure.[153] Colorless oil. **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.39 – 7.32 (m, 4H), 7.32 – 7.28 (m, 1H), 5.72 (s, 1H), 5.08 (d, J = 5.7 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.57 (dd, J = 11.8, 3.3 Hz, 1H), 3.47 (dd, J = 11.8, 8.4 Hz, 1H), 3.35 – 3.20 (m, 1H), 1.27 (t, J = 7.2 Hz, 3H) ppm; **^{13}C NMR** (151 MHz, Chloroform-d) δ 173.2, 139.2, 128.7, 128.3, 126.2, 86.8, 61.4, 56.6, 53.7, 14.2 ppm; **IR** (thin film) 3229, 3065, 3034, 2983, 2942, 2906, 1886, 1813, 1729 cm^{-1}; **MS** (ESI) *m/z* 244.0942 (244.0950 calcd for $C_{12}H_{15}NO_3^+$ $[MH]^+$).



96

***O*-Benzoyl-*N*-propylhydroxylamine (96):** Colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.5, 1.4 Hz, 2H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 3.12 (t, *J* = 7.1 Hz, 2H), 1.66 (h, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 167.1, 133.4, 129.5, 128.7, 128.6, 54.5, 20.7, 11.7 ppm; **IR** (thin film) 3239, 2963, 2936, 2876, 1765, 1716 cm^{-1}; **MS** (ESI) *m/z* 180.0997 (180.1019 calcd for $C_{10}H_{14}NO_2^+$ $[MH]^+$).

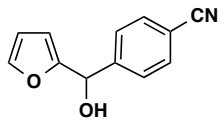
General Procedure for the Synthesis of Furylcarbinols: Furylcarbinols were prepared using standard synthetic chemistry from readily available commercial starting materials.



97

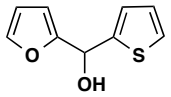
(5-(3-((Benzyloxy)amino)propyl)furan-2-yl)(phenyl)methanol (97): Light yellow oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.47 – 7.42 (m, 2H), 7.39 – 7.28 (m, 8H), 5.94 (d, *J* = 3.1 Hz,

1H), 5.90 (d, *J* = 3.1 Hz, 1H), 5.76 (s, 1H), 4.70 (s, 2H), 2.95 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.85 (tt *J* = 7.3, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.0, 154.5, 141.1, 138.0, 128.5, 128.5, 128.5, 128.0, 127.9, 126.7, 108.4, 105.8, 76.4, 70.2, 51.5, 25.8 ppm; **IR** (thin film) 3382, 3087, 3062, 3030, 2910, 2858, 1955, 1885, 1453, 1190, 1010, 961 cm^{-1}; **MS** (ESI) *m/z* 360.1574 (360.1576 calcd for $C_{21}H_{23}NNaO_3^+$ $[MNa]^+$).



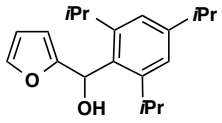
98

4-(Furan-2-yl(hydroxy)methyl)benzonitrile (98): Yellow solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 – 7.63 (m, 2H), 7.59 – 7.54 (m, 2H), 7.42 – 7.38 (m, 1H), 6.36 – 6.31 (m, 1H), 6.15 (d, *J* = 3.3 Hz, 1H), 5.88 (s, 1H), 2.69 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 154.7, 146.0, 143.2, 132.4, 127.3, 118.8, 111.8, 110.6, 108.1, 69.4 ppm; **IR** (thin film) 3418, 3122, 2879, 2228, 1927, 1808, 1609, 1504, 1410, 1141, 1009 cm^{-1}; **MS** (EI^+) *m/z* 199.0628 (199.0633 calcd for $C_{12}H_9O_2^+$ $[M]^+$).



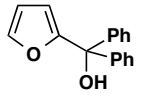
99

Furan-2-yl(thiophen-2-yl)methanol (99): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 3.3 Hz, 1H), 7.38 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.32 (d, *J* = 3.2 Hz, 1H), 6.35 – 6.30 (m, 2H), 6.08 (s, 1H), 4.79 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 171.7, 153.3, 143.1, 142.3, 119.9, 110.6, 108.4, 67.6 ppm; **IR** (thin film) 3119, 2852, 1766, 1621, 1503, 1432 cm^{-1}; MS (EI) *m/z* 180.0247 (180.0245 calcd for $C_9H_8O_2S^+$ $[M]^+$).



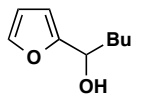
100

Furan-2-yl(2,4,6-triisopropylphenyl)methanol (100): Brown solid; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 (ddd, *J* = 1.8, 0.8, 0.8 Hz, 1H), 7.05 (s, 2H), 6.41 (d, *J* = 2.9 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.00 (ddd, *J* = 3.3, 1.1, 1.1 Hz, 1H), 3.35 (hept, *J* = 6.8 Hz, 2H), 2.89 (hept, *J* = 6.9 Hz, 1H), 2.32 (d, *J* = 3.5 Hz, 1H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 6H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.4, 148.8, 142.0, 131.7, 122.2, 110.5, 106.6, 65.8, 34.3, 29.8, 25.1, 24.1, 24.1 ppm; IR (thin film) 3408, 2959, 2928, 2868, 1768, 1607, 1460, 1362, 1142, 1004 cm^{-1}; **MS** (EI^+) *m/z* 300.2096 (300.2089 calcd for $C_{20}H_{28}O_2^+$ $[M]^+$).



101

Furan-2-yldiphenylmethanol (101): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40 – 7.27 (m, 10H), 6.34 (d, *J* = 1.5 Hz, 1H), 5.94 (d, *J* = 3.2 Hz, 1H), 3.11 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 158.0, 144.7, 142.8, 128.1, 127.8, 127.3, 110.2, 109.8, 78.1 ppm; **IR** (thin film) 3410, 3061, 3028, 1957, 1888, 1813, 1725, 1675, 1598, 1554, 1490, 1447 cm^{-1}; **MS** (EI) *m/z* 250.0991 (250.0994 calcd for $C_{17}H_{14}O_2^+$ $[M]^+$).

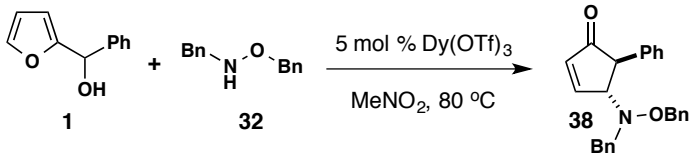


102

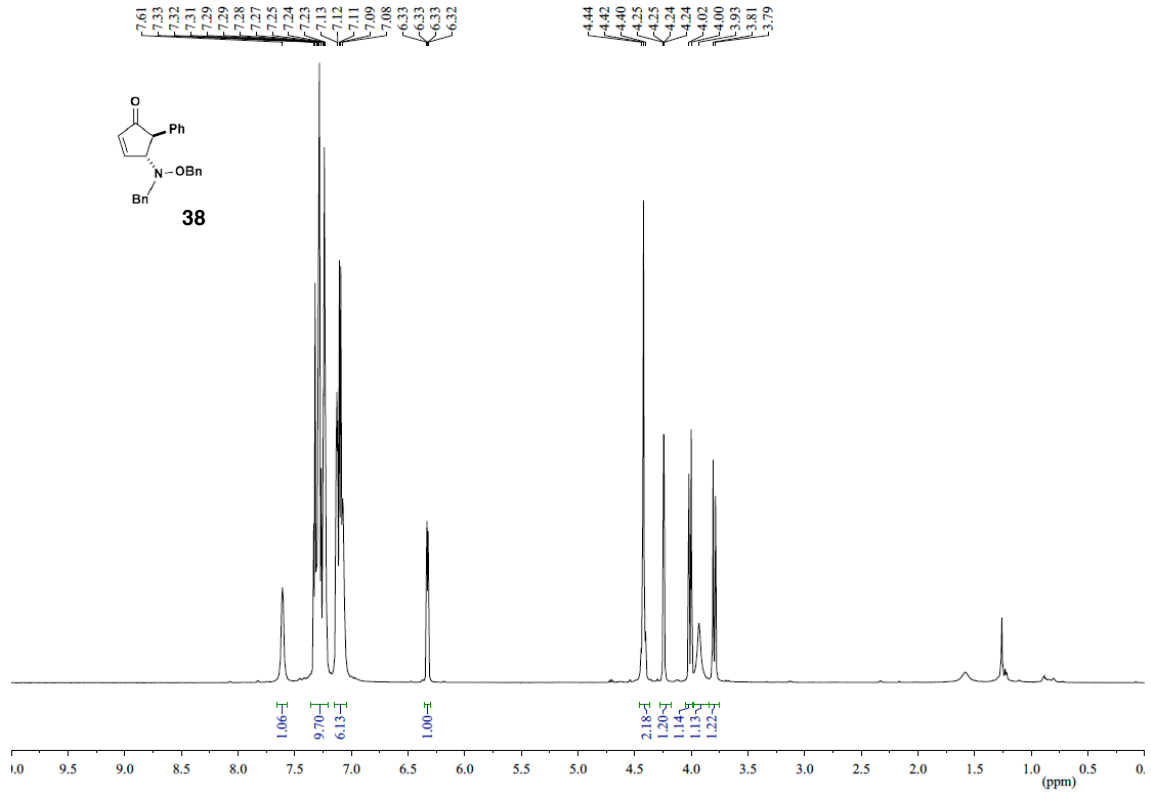
1-(Furan-2-yl)pentan-1-ol (102): Colorless oil; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (m, 1H), 6.32 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 4.66 (td, *J* = 6.7, 3.8 Hz, 1H), 1.91 (s, 1H), 1.88 – 1.80 (m, 2H), 1.47 – 1.23 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H) ppm; **^{13}C**

NMR (125 MHz, $CDCl_3$) δ 157.1, 142.0, 110.2, 105.9, 68.0, 35.4, 27.8, 22.6, 14.1 ppm; **IR** (thin film) 3360, 2956, 2932, 2861, 1597, 1505, 1466, 1149, 1007 cm^{-1}; **MS** (EI^+) *m/z* 154.0998 (154.0994 calcd for $C_9H_{14}O_2^+$ $[M]^+$).

Synthesis of 4-aminocyclopentenones



4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-one (38): According to the general procedure, furan-2-yl(phenyl)methanol (38.2 mg, 0.220 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (46.8 mg, 0.220 mmol) were treated with $Dy(OTf)_3$ (6.7 mg, 0.011 mmol) in $MeNO_2$ (2.2 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **38** (71.6 mg, 88%) as a light orange/yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.36 – 7.20 (m, 9H), 7.15 – 7.04 (m, 6H), 6.33 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.43 (d, *J* = 11.9 Hz, 1H), 4.41 (d, *J* = 10.2 Hz, 1H), 4.24 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 4.01 (d, *J* = 12.6 Hz, 1H), 3.93 (s, 1H), 3.80 (d, *J* = 12.6 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.4, 139.0, 136.7, 136.6, 134.9, 129.9, 129.2, 129.1, 128.5, 128.4, 128.3, 128.3, 127.7, 127.2, 76.9, 73.9, 61.3, 52.7 ppm; **IR** (thin film) 3063, 3031, 2919, 1709, 1595, 1454, 1265, 1029, 975 cm^{-1}; **MS** (ESI) *m/z* 392.1636 (392.1626 calcd for $C_{25}H_{23}NNaO_2^+$ $[MNa]^+$).


7.61
7.33
7.32
7.31
7.29
7.29
7.28
7.27
7.25
7.24
7.23
7.13
7.12
7.11
7.09
7.08
6.33
6.33
6.33
6.32
4.44
4.42
4.40
4.25
4.25
4.24
4.24
4.02
4.00
3.93
3.81
3.79
O
Ph
N
OBn
Bn
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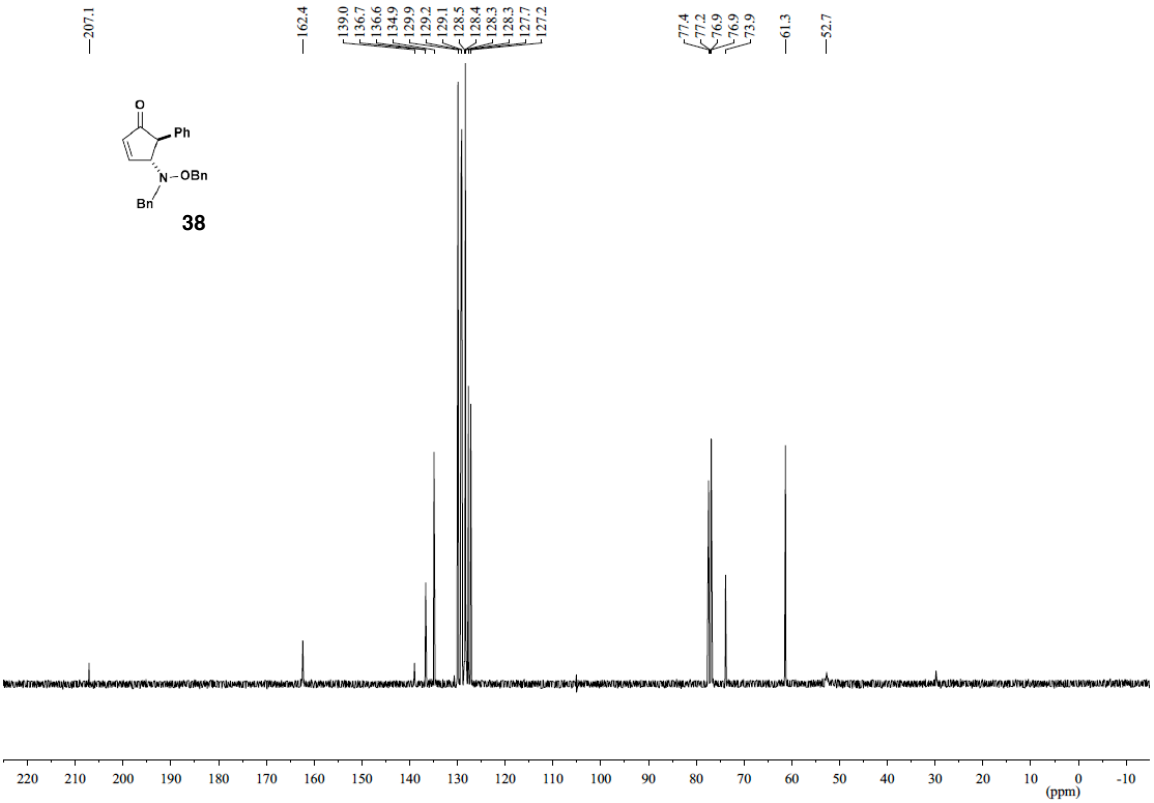
1.06
9.70
6.13
1.00
2.18
1.20
1.14
1.13
1.22
(ppm)


207.1
162.4
139.0
136.7
136.6
134.9
129.9
129.2
129.1
128.5
128.4
128.3
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127.7
127.2
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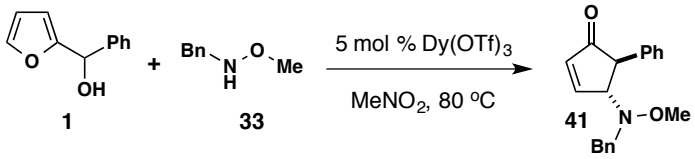
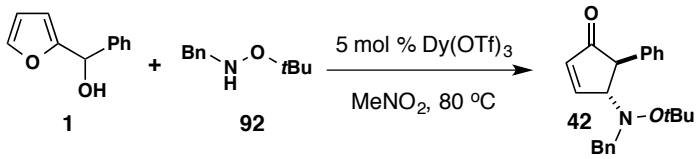
52.7
O
Ph
N
OBn
Bn
38
(ppm)

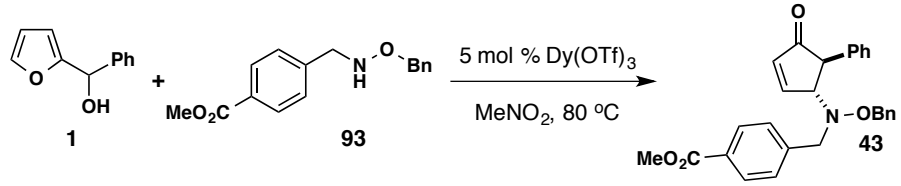


4-(Benzyl(methoxy)amino)-5-phenylcyclopent-2-en-1-one (41): According to the general procedure, furan-2-yl(phenyl)methanol (30.0 mg, 0.172 mmol) and *N*-benzyl-*O*-methylhydroxylamine (**33**) (23.6 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **41** (46.2 mg, 91%) as an orange/brown solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.33 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.23 – 7.21 (m, 3H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.08 (s, 2H), 6.36 (dd, *J* = 5.7, 1.9 Hz, 1H), 4.21 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 3.87 (s, 1H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.32 (s, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.1, 138.9, 136.7, 135.0, 129.7, 129.1, 128.5, 128.3, 127.6, 127.2, 73.9, 62.4, 60.9, 52.9 ppm; **IR** (thin film) 3062, 3030, 2934, 2812, 1709, 1595, 1454, 1266, 1040, 978 cm^{-1}; **MS** (ESI) *m/z* 316.1309 (316.1313 calcd for $C_{19}H_{19}NNaO_2^+$ $[MNa]^+$).



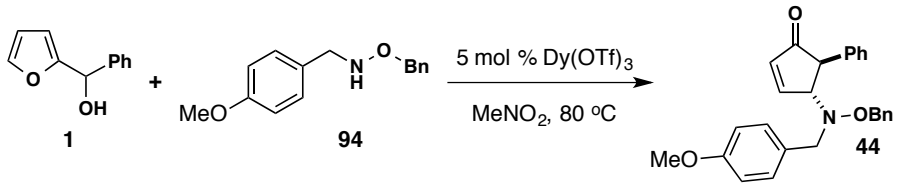
4-(Benzyl(tert-butoxy)amino)-5-phenylcyclopent-2-en-1-one (42): According to the general procedure, furan-2-yl(phenyl)methanol (31.7 mg, 0.182 mmol) and *N*-benzyl-*O*-(*tert*-butyl)hydroxylamine (**92**) (32.7 mg, 0.182 mmol) were treated with $Dy(OTf)_3$ (5.54 mg, 0.0091 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC

for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **42** (46.2 mg, 76%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 1H), 7.35 – 7.25 (m, 3H), 7.19 – 7.03 (m, 5H), 6.79 (d, J = 7.5 Hz, 2H), 6.28 (d, J = 3.6 Hz, 1H), 4.19 – 4.08 (m, 3H), 3.80 (d, J = 12.7 Hz, 1H), 1.22 (s, 9H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.9, 164.9, 140.0, 136.9, 134.1, 129.4, 129.1, 128.7, 128.3, 127.5, 127.1, 78.0, 72.0, 62.8, 51.1, 28.1 ppm; **IR** (thin film) 3062, 3029, 2975, 2928, 2867, 1712, 1602 cm^{-1}; **MS** (ESI) *m/z* 358.1774 (358.1783 calcd for $C_{22}H_{25}NNaO_2^+$ $[MNa]^+$).



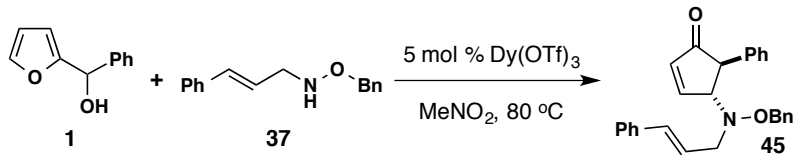
Methyl 4-(((benzyloxy)(4-oxo-5-phenylcyclopent-2-en-1-yl)amino)methyl)benzoate (43): According to the general procedure, furan-2-yl(phenyl)methanol (28.8 mg, 0.166 mmol) and methyl 4-(((benzyloxy)amino)methyl)benzoate (**93**) (44.9 mg, 0.166 mmol) were treated with $Dy(OTf)_3$ (5.1 mg, 0.0084 mmol) in $MeNO_2$ (1.6 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **43** (57.4 mg, 82%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.92 (d, J = 7.8 Hz, 2H), 7.62 (s, 1H), 7.33 (t, J = 7.3 Hz, 2H), 7.31 – 7.27 (m, 4H), 7.18 – 7.13 (m, 2H), 7.13 – 7.08 (m, 4H), 6.35 (dd,

J = 5.8, 1.9 Hz, 1H), 4.47 – 4.37 (m, 2H), 4.24 (d, J = 2.3 Hz, 1H), 4.04 (d, J = 12.8 Hz, 1H), 3.94 (s, 1H), 3.91 (s, 3H), 3.84 (d, J = 12.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.8, 167.0, 162.0, 141.9, 138.8, 136.5, 135.1, 129.8, 129.6, 129.6, 129.2, 129.2, 128.5, 128.5, 128.4, 127.3, 77.0, 74.1, 61.0, 52.7, 52.2 ppm; **IR** (thin film) 3084, 3031, 2950, 2910, 2874, 2275, 1738, 1718, 1701 cm^{-1}; **MS** (ESI) *m/z* 450.1665 (450.1682 calcd for $C_{27}H_{25}NNaO_4^+$ $[MNa]^+$).

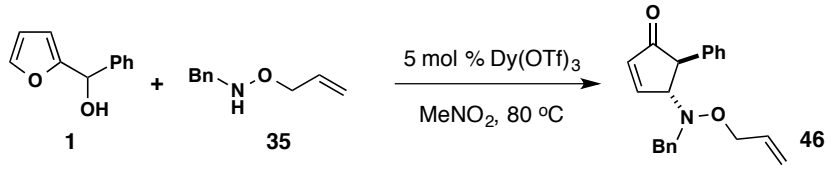


4-((Benzyloxy)(4-methoxybenzyl)amino)-5-phenylcyclopent-2-en-1-one (44): According to the general procedure, furan-2-yl(phenyl)methanol (19.7 mg, 0.113 mmol) and *O*-benzyl-*N*-(4-methoxybenzyl)hydroxylamine (**94**) (27.6 mg, 0.113 mmol) were treated with $Dy(OTf)_3$ (3.4 mg, 0.0057 mmol) in $MeNO_2$ (1.1 mL). The resulting reaction mixture was heated to 80 ºC for 2h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **44** (34.4 mg, 76%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.36 – 7.26 (m, 6H), 7.20 – 7.14 (m, 2H), 7.11 (d, J = 7.5 Hz, 2H), 6.95 (s, 2H), 6.76 (d, J = 8.1 Hz, 2H), 6.33 (dd, J = 5.8, 2.1 Hz, 1H), 4.44 (s, 2H), 4.24 (d, J = 2.5 Hz, 1H), 3.96 (d, J = 12.5 Hz, 1H), 3.94 (s, 1H), 3.78 (s, 3H), 3.74 (d, J = 12.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.2, 162.6, 159.2, 139.1, 136.8, 134.9, 131.1, 129.3, 129.1, 128.7, 128.6, 128.4, 128.3, 127.2, 113.7, 76.8,

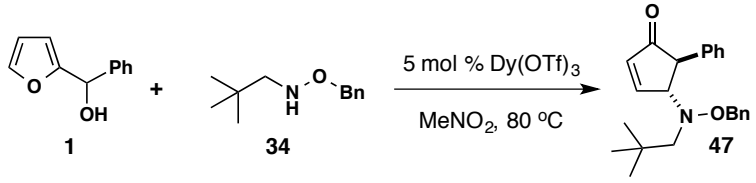
73.6, 60.6, 55.4, 52.8 ppm; **IR** (thin film) 3030, 2930, 2837, 1884, 1712, 1611, 1513 cm^{-1}; **MS** (ESI) *m/z* 422.1716 (422.1732 calcd for $C_{26}H_{25}NNaO_3^+$ $[MNa]^+$).



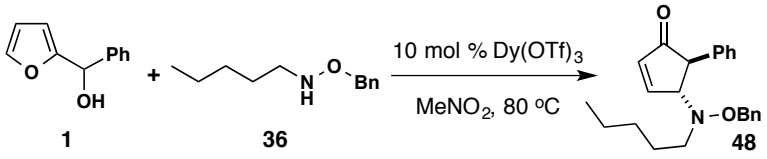
4-((Benzyloxy)(cinnamyl)amino)-5-phenylcyclopent-2-en-1-one (45): According to the general procedure, furan-2-yl(phenyl)methanol (15.0 mg, 0.086 mmol) and *O*-benzyl-*N*-cinnamylhydroxylamine (**37**) (20.6 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 1.5 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **45** (29.3 mg, 86%) as a light orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.35 – 7.19 (m, 11H), 7.16 (d, *J* = 7.4 Hz, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 6.33 (dd, *J* = 5.8, 2.0 Hz, 1H), 6.12 (ddd, *J* = 14.7, 6.6, 6.6 Hz, 1H), 5.90 (d, *J* = 15.9 Hz, 1H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.63 (d, *J* = 10.8 Hz, 1H), 4.37 (s, 1H), 3.87 (s, 1H), 3.69 (dd, *J* = 12.8, 6.1 Hz, 1H), 3.48 (dd, *J* = 13.0, 8.1 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 162.5, 139.0, 136.8, 136.7, 134.9, 134.9, 129.2, 129.1, 128.6, 128.6, 128.5, 128.3, 127.9, 127.2, 126.5, 123.9, 76.8, 73.6, 59.3, 52.4 ppm; **IR** (thin film) 3061, 3029, 2822, 2854, 1950, 1709, 1495, 1453, 1165, 1028, 968 cm^{-1}; **MS** (ESI) *m/z* 418.1766 (418.1783 calcd for $C_{27}H_{25}NNaO_2^+$ $[MNa]^+$).



4-((Allyloxy)(benzyl)amino)-5-phenylcyclopent-2-en-1-one (46): According to the general procedure, furan-2-yl(phenyl)methanol (100.0 mg, 0.57 mmol) and *O*-allyl-*N*-benzylhydroxylamine (**35**) (93.8 mg, 0.57 mmol) were treated with $Dy(OTf)_3$ (17.5 mg, 0.029 mmol) in $MeNO_2$ (5.7 mL). The resulting reaction mixture was heated to 80 ºC for 45 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **46** (173.5 mg, 95%) as an orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 6.0, 2.5 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29 – 7.24 (m, 1H), 7.23 – 7.18 (m, 3H), 7.12 (d, *J* = 7.3 Hz, 2H), 7.07 (s, 2H), 6.36 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.70 (dddd, *J* = 16.8, 10.3, 6.2, 6.2 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.25 – 4.19 (m, 1H), 4.02 (d, *J* = 12.7 Hz, 1H), 4.00 – 3.89 (m, 3H), 3.78 (d, *J* = 12.7 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.1, 162.3, 138.9, 136.6, 135.0, 133.5, 129.8, 129.1, 128.5, 128.3, 127.6, 127.2, 118.3, 75.9, 73.8, 61.4, 52.8 ppm; **IR** (thin film) 3063, 3029, 2916, 2858, 1708, 1495, 1454, 1165, 1029, 980 cm^{-1}; **MS** (ESI) *m/z* 342.1466 (342.1470 calcd for $C_{21}H_{21}NNaO_2^+$ $[MNa]^+$).

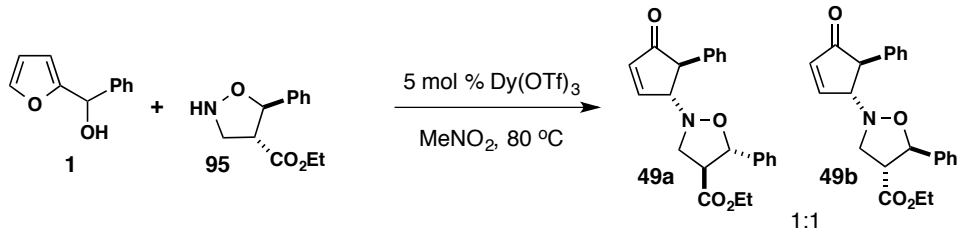


4-((Benzyloxy)(neopentyl)amino)-5-phenylcyclopent-2-en-1-one (47): According to the general procedure, furan-2-yl(phenyl)methanol (30.0 mg, 0.172 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (**34**) (33.3 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0085 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 45 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **47** (52.6 mg, 81%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.35 – 7.30 (m, 2H), 7.30 – 7.22 (m, 4H), 7.17 – 7.09 (m, 4H), 6.40 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.70 (d, *J* = 10.5 Hz, 1H), 4.62 (d, *J* = 10.5 Hz, 1H), 4.38 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.72 (d, *J* = 2.8 Hz, 1H), 2.65 (d, *J* = 14.1 Hz, 1H), 2.58 (d, *J* = 14.1 Hz, 1H), 0.94 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.3, 162.2, 139.2, 136.6, 135.4, 129.0, 128.7, 128.5, 128.3, 128.1, 127.1, 76.5, 75.1, 67.8, 53.5, 31.7, 28.5 ppm; **IR** (thin film) 3063, 3030, 2952, 2866, 1711, 1601, 1453, 1362, 1026, 981 cm^{-1}; **MS** (ESI) *m/z* 372.1932 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



4-((Benzyloxy)(pentyl)amino)-5-phenylcyclopent-2-en-1-one (48): According to the general procedure, furan-2-yl(phenyl)methanol (15.0 mg, 0.086 mmol) and *O*-benzyl-*N*-pentylhydroxylamine (**36**) (16.7 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (0.9 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and

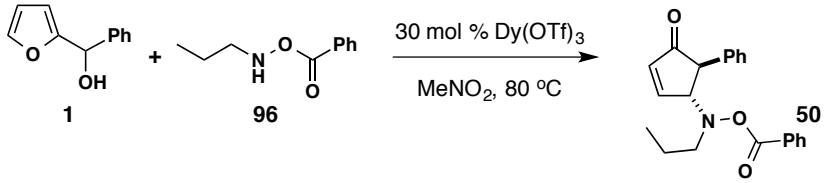
extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **48** (22.8 mg, 76%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.32 (ddd, *J* = 7.7, 4.1 Hz, 5H), 7.27 – 7.22 (m, 3H), 7.13 – 7.08 (m, 2H), 6.36 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.69 (d, *J* = 10.6 Hz, 1H), 4.64 (d, *J* = 10.7 Hz, 1H), 4.27 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.77 (s, 1H), 2.87 (ddd, *J* = 12.5, 8.9, 5.6 Hz, 1H), 2.67 (ddd, *J* = 12.5, 8.8, 5.9 Hz, 1H), 1.57 – 1.41 (m, 2H), 1.29 – 1.20 (m, 4H), 0.89 – 0.81 (m, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.3, 162.2, 139.1, 136.8, 135.0, 129.1, 128.9, 128.5, 128.3, 128.3, 127.1, 77.2, 75.1, 57.4, 52.8, 29.5, 27.1, 22.6, 14.1 ppm; **IR** (thin film) 3062, 3029, 2954, 2982, 2858, 1711, 1496, 1453, 1165, 1029, 982 cm^{-1}; **MS** (ESI) *m/z* 372.1937 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



Ethyl 2-(4-oxo-5-phenylcyclopent-2-en-1-yl)-5-phenylisoxazolidine-4-carboxylate (49a,b): According to the general procedure, furan-2-yl(phenyl)methanol (33.7 mg, 0.194 mmol) and ethyl 5-phenylisoxazolidine-4-carboxylate **95** (42.9 mg, 0.194 mmol) were treated with $Dy(OTf)_3$ (5.9 mg, 0.0097 mmol) in $MeNO_2$ (1.9 mL). The resulting reaction mixture was heated to 80 ºC for 1.25 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **49a,b**

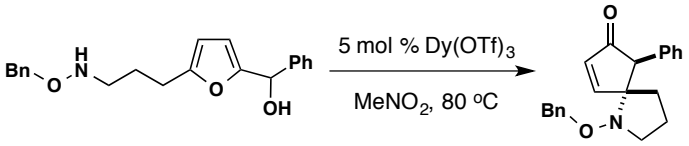
(46.0 mg, 63%, 1:1 mixture of diastereomers) as a brown oil. Higher RF diastereomer **^{1}H NMR** (500 MHz, Toluene-d_8, 90 ºC) δ 7.45 – 7.30 (m, 3H), 7.21 – 6.94 (m, 8H), 6.02 (d, J = 5.8 Hz, 1H), 5.33 (d, J = 5.9 Hz, 1H), 4.09 (s, 1H), 3.94 – 3.75 (m, 2H), 3.52 (s, 1H), 3.19 – 3.08 (m, 2H), 3.08 – 3.00 (m, 1H), 3.04 (t, J = 8.1 Hz, 1H), 0.88 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (200 MHz, Toluene-d_8, 70 ºC) 204.0, 171.6, 170.0, 159.8, 135.4, 129.2, 129.1, 128.6, 127.5, 126.8, 125.7, 81.8, 74.3, 61.3, 60.2, 57.0, 56.8, 56.1, 14.3 ppm; **IR** (thin film) 3063, 3030, 2981, 2927, 2852, 1714, 1597 cm^{-1}; **MS** (ESI) *m/z* 400.1516 (400.1525 calcd for $C_{23}H_{23}NNaO_4^+$ $[MNa]^+$).

Lower RF diastereomer **^{1}H NMR** (500 MHz, Toluene-d_8, 90 ºC) δ 7.32 (d, J = 7.1 Hz, 3H), 7.19 – 7.10 (m, 2H), 7.10 – 6.95 (m, 6H), 6.02 (dd, J = 5.8, 1.6 Hz, 1H), 5.18 (d, J = 6.5 Hz, 1H), 4.06 (q, J = 2.5 Hz, 1H), 3.90 (dddd, J = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 3.58 (d, J = 3.1 Hz, 1H), 3.37 (dd, J = 9.4, 5.2 Hz, 1H), 3.06 (ddd, J = 8.7, 6.5, 5.1 Hz, 1H), 2.78 (t, J = 9.1 Hz, 1H), 0.92 (t, J = 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, Toluene-d_8, 90 ºC) 203.9, 171.5, 159.5, 159.3, 141.2, 139.4, 135.6, 135.6, 127.4, 127.0, 100.8, 82.1, 74.9, 61.3, 57.0, 56.5, 56.2, 24.5, 14.4 ppm; **IR** (thin film) 3063, 3030, 2981, 2925, 2852, 1714, 1597 cm^{-1}; **MS** (ESI) *m/z* 400.1508 (400.1525 calcd for $C_{23}H_{23}NNaO_4^+$ $[MNa]^+$).



4-((Benzoyloxy)(propyl)amino)-5-phenylcyclopent-2-en-1-one (50): According to the general procedure, furan-2-yl(phenyl)methanol (28.3 mg, 0.163 mmol) and *O*-benzoyl-*N*-propylhydroxylamine (**96**) (29.1 mg, 0.163 mmol) were treated with 30 mol % Dy(OTf)$_3$ (29.8 mg, 0.0489 mmol) in MeCN (1.6 mL). The resulting reaction mixture was stirred at

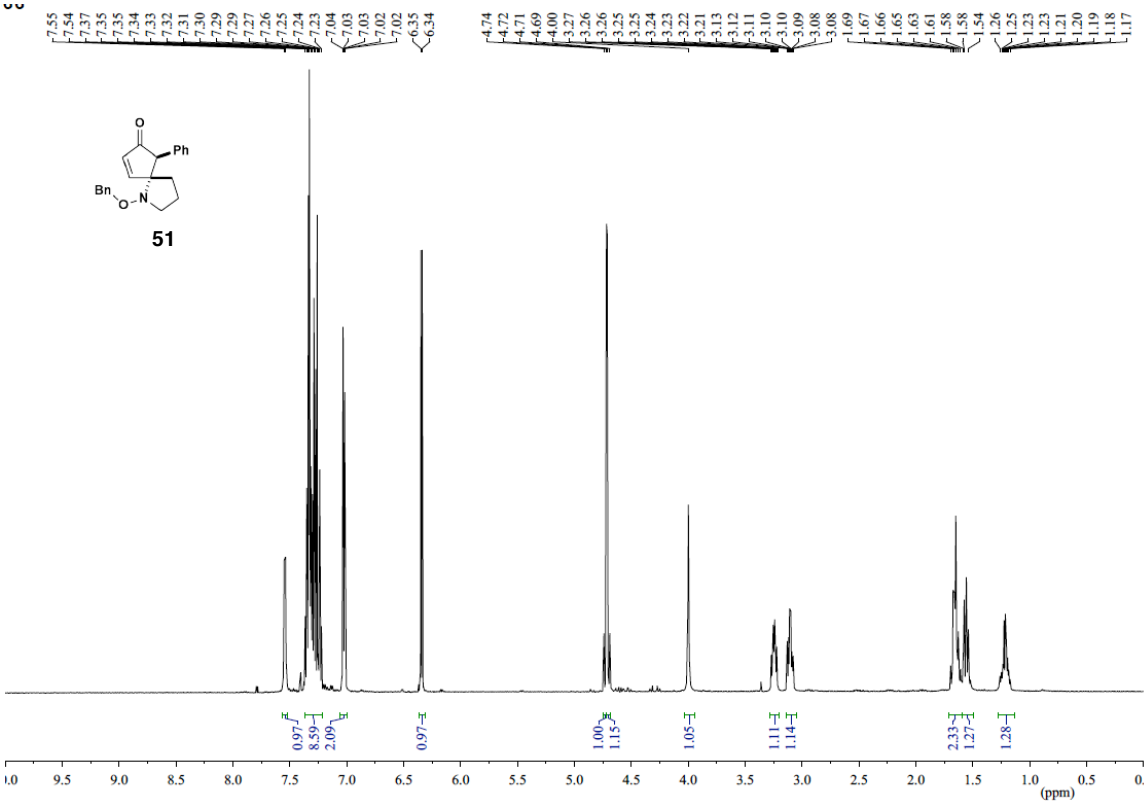
room temperature for 58 h. The reaction was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **50** (27.1 mg, 50%) as a yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.84 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.58 (dddd, *J* = 7.1, 7.1, 1.3, 1.3 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.25 (m, 1H), 7.20 – 7.14 (m, 2H), 6.36 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.56 (dd, *J* = 4.6, 2.3 Hz, 1H), 3.89 (d, *J* = 2.8 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.91 (ddd, *J* = 12.7, 8.2, 6.8 Hz, 1H), 1.61 – 1.48 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 206.2, 165.7, 160.9, 138.4, 135.7, 133.6, 129.6, 129.3, 128.7, 128.5, 128.2, 127.5, 76.0, 59.6, 52.7, 20.6, 11.6 ppm; **IR** (thin film) 3063, 3030, 2964, 2935, 2876, 1743, 1712 cm^{-1}; **MS** (ESI) *m/z* 358.1406 (358.1419 calcd for $C_{21}H_{21}NNaO_3^+$ $[MNa]^+$).

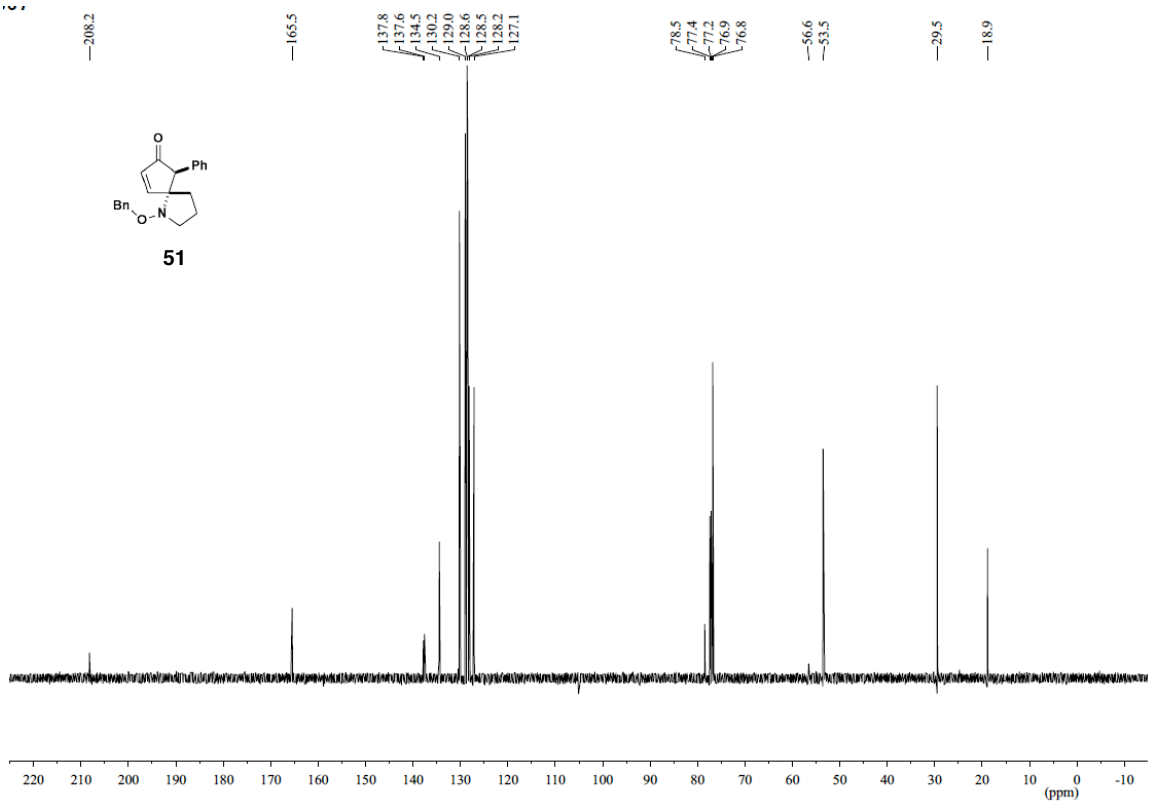


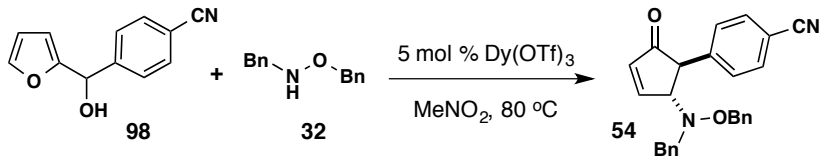
97 51

1-(Benzyloxy)-6-phenyl-1-azaspiro[4.4]non-8-en-7-one (51): According to the general procedure, (5-(3-((benzyloxy)amino)propyl)furan-2-yl)(phenyl)methanol (**97**) (240 mg, 0.71 mmol) was treated with $Dy(OTf)_3$ (21.6 mg, 0.036 mmol) in $MeNO_2$ (7 mL). The resulting reaction mixture was heated to 80 ºC for 1 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **51** (185.6 mg, 82%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 5.8 Hz, 1H),

7.38 – 7.21 (m, 8H), 7.06 – 7.00 (m, 2H), 6.34 (d, J = 5.8 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.70 (d, J = 11.4 Hz, 1H), 4.00 (s, 1H), 3.28 – 3.20 (m, 1H), 3.10 (ddd, J = 10.2, 8.0, 4.3 Hz, 1H), 1.71 – 1.59 (m, 2H), 1.60 – 1.50 (m, 1H), 1.28 – 1.13 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 208.2, 165.5, 137.8, 137.6, 134.5, 130.2, 129.0, 128.6, 128.5, 128.2, 127.1, 78.5, 76.8, 56.6, 53.5, 29.5, 18.9 ppm; **IR** (thin film) 3061, 3029, 2940, 2865, 1707, 1594, 1496, 1453, 1342, 1208, 1032, 977, 918 cm^{-1}; **MS** (ESI) *m/z* 342.1477 (342.1470 calcd for $C_{21}H_{21}NNaO_2^+$ $[MNa]^+$).





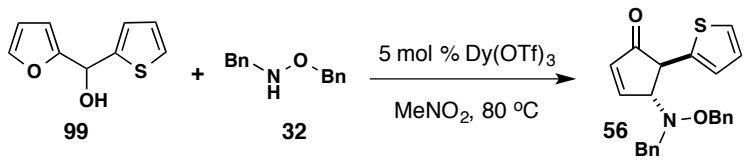


4-(2-(Benzyl(benzyloxy)amino)-5-oxocyclopent-3-en-1-yl)benzonitrile (54): According to the general procedure, 4-(furan-2-yl(hydroxy)methyl)benzonitrile (34.4 mg, 0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (36.8 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 17 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **54** (57.0 mg, 84%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.63 – 7.56 (m, 3H), 7.32 – 7.22 (m, 6H),

7.16 (d, J = 8.1 Hz, 2H), 7.15 – 7.10 (m, 2H), 7.07 (s, 2H), 6.32 (dd, J = 5.8, 2.0 Hz, 1H), 4.45 (d, J = 10.9 Hz, 1H), 4.43 (d, J = 10.9 Hz, 1H), 4.22 (ddd, J = 2.3 Hz, 1H), 4.00 (d, J = 12.6 Hz, 1H), 3.95 (s, 1H), 3.78 (d, J = 12.5 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.3, 162.3, 144.3, 136.5, 136.2, 134.7, 132.7, 129.6, 129.4, 129.4, 128.5, 128.5, 128.4, 128.0, 118.8, 111.1, 76.8, 73.1, 61.1, 52.6 ppm; **IR** (thin film) 3063, 3031, 2919, 2866, 2227, 1708, 1607, 1454, 1276, 1163, 1028, 972 cm^{-1}; **MS** (ESI) *m/z* 417.1573 (417.1579 calcd for $C_{26}H_{22}N_2NaO_2^+$ $[MNa]^+$).

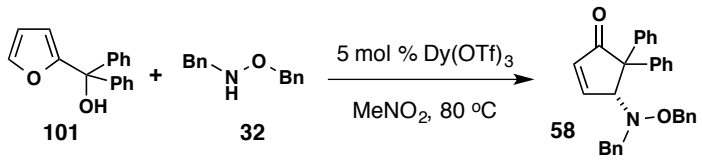
4-(Benzyl(benzyloxy)amino)-5-(4-methoxyphenyl)cyclopent-2-en-1-one (55): According to the general procedure, furan-2-yl(4-methoxyphenyl)methanol (23.1 mg, 0.113 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (24.1 mg, 0.113 mmol) were treated with $Dy(OTf)_3$ (3.4 mg, 0.0057 mmol) in $MeNO_2$ (1.1 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **55** (36.7 mg, 81%) as a yellow waxy solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.31 – 7.27 (m, 3H), 7.28 – 7.23 (m, 3H), 7.15 – 7.09 (m, 4H), 7.02 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 6.32 (dd, J = 5.8, 1.9 Hz, 1H), 4.41 (s, 2H), 4.21 (dd, J = , 4.2, 2.1 Hz, 1H), 4.01 (d, J = 12.6 Hz, 1H), 3.88 (s, 1H), 3.81 (d, J = 12.6 Hz, 1H), 3.80 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.4, 162.2, 158.8, 136.7, 136.7, 134.9, 130.9, 130.0, 129.5, 129.3, 128.4, 128.4, 128.3,

127.7, 114.6, 77.0, 73.9, 61.4, 55.5, 52.0 ppm; **IR** (thin film) 3030, 2921, 2854, 1883, 1708, 1611, 1511 cm^{-1}; **MS** (ESI) *m/z* 422.1717 (422.1732 calcd for $C_{26}H_{25}NNaO_3^+$ $[MNa]^+$).

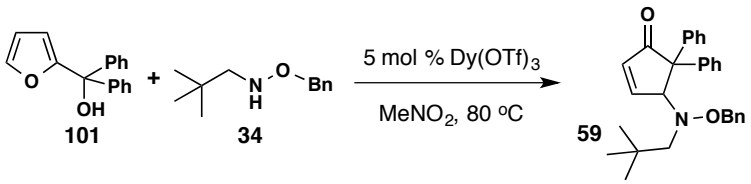


4-(Benzyl(benzyloxy)amino)-5-(thiophen-2-yl)cyclopent-2-en-1-one (56): According to the general procedure, furan-2-yl(thiophen-2-yl)methanol (31.1 mg, 0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (36.8 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 30 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **56** (59.2 mg, 92%) as a brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.32 – 7.27 (m, 6H), 7.25 – 7.19 (m, 3H), 7.14 – 7.10 (m, 2H), 7.00 – 6.96 (m, 1H), 6.90 (d, *J* = 3.3 Hz, 1H), 6.31 (dd, *J* = 6.0, 1.8 Hz, 1H), 4.43 (d, *J* = 10.6 Hz, 1H), 4.40 (d, *J* = 10.6 Hz, 1H), 4.34 (ddd, *J* = 2.4, 2.4, 2.4 Hz, 1H), 4.20 (s, 1H), 4.06 (d, *J* = 12.7 Hz, 1H), 3.95 (d, *J* = 12.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 204.7, 161.4, 140.1, 136.7, 136.5, 134.1, 129.9, 129.2, 128.6, 128.4, 128.3, 127.8, 127.2, 125.9, 124.7, 77.0, 74.1, 61.4, 47.6 ppm; **IR** (thin film) 3064, 3030, 2919, 2867, 1954, 1712, 1454, 1343, 1167, 1028, 972 cm^{-1}; **MS** (ESI) *m/z* 398.1188 (398.1191 calcd for $C_{23}H_{21}NNaO_2S^+$ $[MNa]^+$).

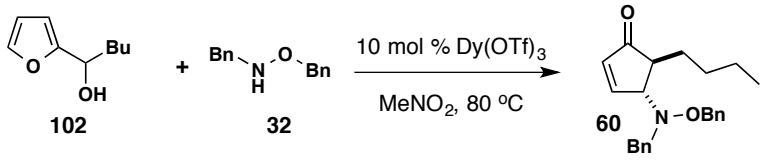
(4R,5S)-4-(Benzyl(benzyloxy)amino)-5-(2,4,6-triisopropylphenyl)cyclopent-2-en-1-one (57): According to the general procedure, furan-2-yl(2,4,6-triisopropylphenyl)methanol (32.0 mg, 0.105 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (22.5 mg, 0.105 mmol) were treated with $Dy(OTf)_3$ (3.2 mg, 0.0053 mmol) in $MeNO_2$ (1.0 mL). The resulting reaction mixture was heated to 80 ºC for 40 min. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **57** (41.7 mg, 80%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.28 (d, *J* = 7.3 Hz, 2H), 7.17 – 7.13 (m, 1H), 7.11 (t, *J* = 7.4 Hz, 2H), 7.07 (d, *J* = 1.9 Hz, 1H), 6.90 (d, *J* = 1.9 Hz, 1H), 6.67 (s, 2H), 6.31 (d, *J* = 4.7 Hz, 1H), 4.66 (d, *J* = 11.2 Hz, 1H), 4.63 – 4.53 (m, 2H), 4.03 (s, 1H), 3.99 (d, *J* = 12.2 Hz, 1H), 3.65 (d, *J* = 12.2 Hz, 1H), 3.57 (p, *J* = 6.8 Hz, 1H), 2.91 (hept, *J* = 6.9 Hz, 1H), 1.83 (hept, *J* = 6.7 Hz, 1H), 1.44 (d, *J* = 6.6 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 6H),z 1.25 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.65 (d, *J* = 5.6 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.4, 160.9, 147.9, 147.7, 137.3, 136.3, 134.4, 130.7, 129.7, 129.2, 128.4, 128.3, 128.2, 127.5, 122.5, 121.4, 76.2, 72.6, 60.1, 48.3, 34.4, 30.7, 30.3, 29.9, 26.5, 24.4, 24.3, 24.2, 24.1, 22.2 ppm; **IR** (thin film) 3063, 3032, 2960, 2926, 2868, 1710, 1607 cm^{-1}; **MS** (ESI) *m/z* 518.3011 (518.3035 calcd for $C_{34}H_{41}NNaO_2^+$ $[MNa]^+$).



4-(Benzyl(benzyloxy)amino)-5,5-diphenylcyclopent-2-en-1-one (58): According to the general procedure, furan-2-yldiphenylmethanol (43.2 mg, 0.173 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (36.8 mg, 0.173 mmol) were treated with $Dy(OTf)_3$ (5.3 mg, 0.0087 mmol) in $MeNO_2$ (1.7 mL). The resulting reaction mixture was heated to 80 ºC for 4 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **58** (58.4 mg, 76%) as a yellow oil. **^{1}H NMR** (500 MHz, Toluene-d_8, 90 °C) δ 7.58 (dd, *J* = 6.1, 2.8 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.30 – 7.19 (m, 2H), 7.13 – 7.09 (m, 2H), 7.08 – 6.89 (m, 11H), 6.79 (d, *J* = 6.7 Hz, 2H), 6.32 (s, 1H), 6.02 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.96 (s, 1H), 3.95 (d, *J* = 11.0 Hz, 1H), 3.76 (d, *J* = 10.9 Hz, 1H), 3.49 (dd, *J* = 20.3, 12.9 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, Toluene-d_8, 90 °C) δ 205.0, 143.5, 142.1, 138.3, 135.3, 132.0, 131.8, 130.5, 130.4, 130.4, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.3, 127.0, 75.8, 75.5, 63.6, 60.7 ppm; **IR** (thin film) 3087, 3060, 3030, 2922, 2858, 1952, 1883, 1808, 1709 cm^{-1}; **MS** (ESI) *m/z* 468.1920 (468.1940 calcd for $C_{31}H_{27}NNaO_2^+$ $[MNa]^+$).

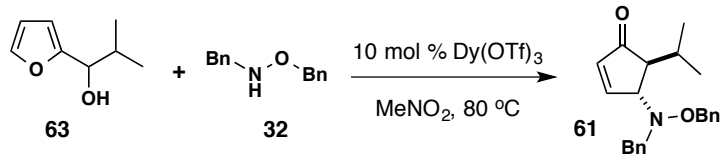


4-((Benzyloxy)(neopentyl)amino)-5,5-diphenylcyclopent-2-en-1-one (59): According to the general procedure, furan-2-yldiphenylmethanol (100.0 mg, 0.40 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (**34**) (77.2 mg, 0.40 mmol) were treated with $Dy(OTf)_3$ (12.2 mg, 0.020 mmol) in $MeNO_2$ (4.0 mL). The resulting reaction mixture was heated to 80 ºC for 18 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **59** (142.0 mg, 83%) as a brown/orange solid. **^{1}H NMR** (500 MHz, toluene-d_8, 80 °C) δ 7.58 (dd, *J* = 6.1, 2.7 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.03 (m, 11H) 6.02 (dd, *J* = 6.0, 1.4 Hz, 1H), 4.92 (s, 1H), 4.28 (d, *J* = 11.1 Hz, 1H), 3.86 (s, 1H), 2.55 (d, *J* = 13.9 Hz, 1H), 2.25 (d, *J* = 13.8 Hz, 1H), 0.71 (s, 9H) ppm; **^{13}C NMR** (125 MHz, toluene-d_8, 80 °C) δ 204.5, 158.1, 143.9, 141.3, 138.0, 135.0, 131.8, 131.6, 128.5, 128.4, 128.2, 127.6, 126.9, 126.7, 77.2, 73.2, 67.7, 62.9, 31.7, 28.7, 24.2 ppm; **IR** (thin film) 3059, 2953, 2868, 1707, 1494, 1444, 1265, 1037, 1029, 949 cm^{-1}; **MS** (ESI) *m/z* 448.2231 (448.2252 calcd for $C_{29}H_{31}NNaO_2^+$ $[MNa]^+$).



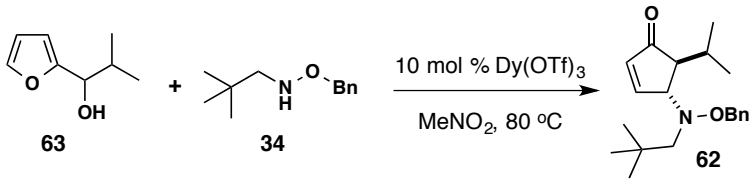
4-(Benzyl(benzyloxy)amino)-5-butylcyclopent-2-en-1-one (60): According to the general procedure, 1-(furan-2-yl)pentan-1-ol (26.5 mg, 0.172 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (36.7 mg, 0.172 mmol) were treated with $Dy(OTf)_3$ (10.5 mg, 0.0172 mmol) in $MeNO_2$ (1.8 mL). The resulting reaction mixture was heated to 80 ºC for 48 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and

extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **60** (31.8 mg, 53%) as a dark yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 5.9, 2.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.29 – 7.24 (m, 3H), 7.11 – 7.05 (m, 2H), 6.26 (dd, *J* = 5.8, 1.4 Hz, 1H), 4.34 (s, 2H), 3.98 (d, *J* = 12.9 Hz, 1H), 3.95 (d, *J* = 13.1 Hz, 1H), 3.91 (s, 1H), 2.53 (s, 1H), 1.76 – 1.65 (m, 1H), 1.63 – 1.51 (m, 1H), 1.35 – 1.23 (m, 4H), 0.88 (dd, *J* = 6.9 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.9, 160.8, 137.4, 136.7, 135.7, 129.8, 129.1, 128.5, 128.4, 128.2, 127.8, 76.9, 71.7, 60.7, 47.2, 30.0, 28.9, 23.0, 14.0 ppm; **IR** (thin film) 3063, 3031, 2955, 2928, 2858, 1707, 1454, 1359, 1176, 1028, 976 cm^{-1}; **MS** (ESI) *m/z* 372.1941 (372.1939 calcd for $C_{23}H_{27}NNaO_2^+$ $[MNa]^+$).



(4-(Benzyl(benzyloxy)amino)-5-isopropylcyclopent-2-en-1-one (61): According to the general procedure, 1-(furan-2-yl)-2-methylpropan-1-ol (12.1 mg, 0.086 mmol) and *N*,*O*-dibenzylhydroxylamine (**32**) (18.4 mg, 0.086 mmol) were treated with $Dy(OTf)_3$ (5.2 mg, 0.0086 mmol) in $MeNO_2$ (0.9 mL). The resulting reaction mixture was heated to 80 ºC for 24 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **61** (14.4 mg, 50%) as a light orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.7, 2.1 Hz, 1H), 7.36 (m, 5H), 7.28 – 7.22 (m, 3H), 7.09

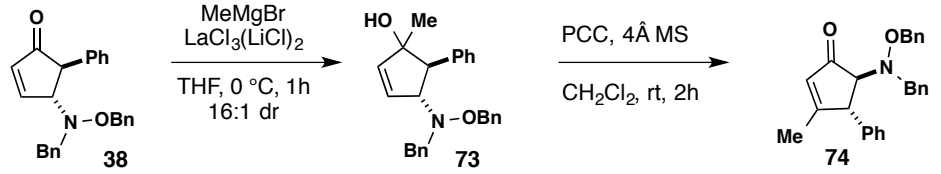
– 7.01 (m, 2H), 6.26 (dd, J = 5.8, 1.3 Hz, 1H), 4.33 (s, 2H), 4.00 – 3.87 (m, 3H), 2.41 (s, 1H), 2.19 (dqq, J = 13.9, 6.9, 4.5 Hz, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.7, 160.8, 137.5, 136.7, 136.6, 129.8, 129.1, 128.5, 128.4, 128.2, 127.8, 77.0, 68.9, 60.5, 52.9, 29.0, 20.2, 18.8 ppm; **IR** (thin film) 3063, 3031, 2957, 2928, 2872, 1703, 1454, 1367, 1181, 1028, 963 cm^{-1}; **MS** (ESI) *m/z* 358.1787 (358.1783 calcd for $C_{22}H_{25}NNaO_2^+$ $[MNa]^+$).



4-((Benzyloxy)(neopentyl)amino)-5-isopropylcyclopent-2-en-1-one (62): According to the general procedure, 1-(furan-2-yl)-2-methylpropan-1-ol (20.0 mg, 0.140 mmol) and *O*-benzyl-*N*-neopentylhydroxylamine (**34**) (27.6 mg, 0.140 mmol) were treated with $Dy(OTf)_3$ (8.7 mg, 0.014 mmol) in $MeNO_2$ (1.4 mL). The resulting reaction mixture was heated to 80 ºC for 96 h. The reaction was then quenched at 23 ºC with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford cyclopentenone **62** (22.6 mg, 51%) as an orange oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, J = 5.8, 2.1 Hz, 1H), 7.36 – 7.27 (m, 5H), 6.27 (dd, J = 5.9, 1.6 Hz, 1H), 4.79 (d, J = 10.6 Hz, 1H), 4.73 (d, J = 10.6 Hz, 1H), 4.15 (s, 1H), 2.55 (d, J = 14.3 Hz, 1H), 2.34 (d, J = 14.0 Hz, 1H), 2.27 (dqq, J = 13.8, 6.9, 4.1 Hz, 1H), 2.15 (s, 1H), 1.04 (d, J = 7.0 Hz, 3H), 0.97 (s, 9H), 0.87 (d, J = 6.8 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 209.5, 161.9, 137.0, 136.8, 128.6, 128.5, 128.1, 74.6, 69.1, 66.0, 53.4, 31.6, 28.8,

28.6, 20.5, 18.6 ppm; **IR** (thin film) 3065, 3032, 2955, 2870, 1705, 1463, 1362, 1027, 976 cm^{-1}; **MS** (ESI) *m/z* 338.2093 (338.2096 calcd for $C_{20}H_{29}NNaO_2^+$ $[MNa]^+$).

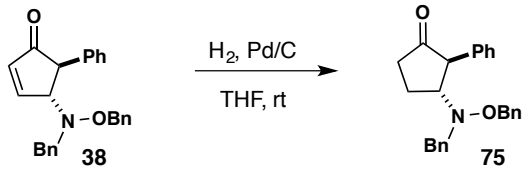
Selected Functionalization of the Cyclopentenone Scaffold



5-(Benzyl(benzyloxy)amino)-3-methyl-4-phenylcyclopent-2-en-1-one (74): Adapted from literature procedure.[151] In a flame dried round bottom flask with magnetic stirrer under N_2 atmosphere, 4-(benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-one **38** was dissolved in 0.5 mL dry THF followed by the addition of 0.6 M $LaCl_3(LiCl)_2$ in THF (0.0939 mmol, 157 µL) and stirring at room temperature for 1 hour. The reaction mixture was cooled to 0 ºC and 3.0 M methylmagnesium bromide in diethyl ether (0.188 mmol, 63 µL) was added. Stirring at 0 ºC continued until complete as determined by thin layer chromatography. Upon completion, the reaction was quenched with saturated aqueous NH_4Cl (5 mL) then extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The crude reaction mixture contained allylic alcohol **73** in 16:1 dr as determined by ^1H NMR spectroscopy**.** The crude reaction mixture was passed through a silica gel plug using 3:1 hexanes : ethyl acetate and used as is for the subsequent reaction. 80% Yield of crude material.

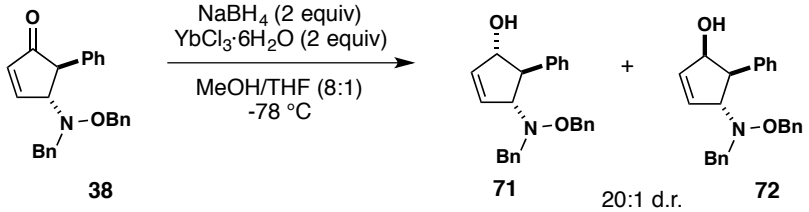
Adapted from literature procedure.[154] In a 10 mL round bottom flask containing a magnetic stir bar under N_2 atmosphere, 4Å mol sieves (500 mg) and pyridinium chlorochromate (PCC) (27.2 mg, 0.126 mmol) were added to anhydrous CH_2Cl_2 (1 mL)

followed by addition of 4-(benzyl(benzyloxy)amino)-1-methyl-5-phenylcyclopent-2-en-1-ol **73** (24.3 mg, 0.063 mmol). Reaction was stirred until complete (2 h) as determined by thin layer chromatography. Upon completion, 5 mL Et_2O was added, and the residual solids were decanted off (3 x). The decanted liquid was transferred to a separatory funnel containing 5 mL 2M NaOH and extracted with Et_2O (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography (1% EtOAc in toluene) to afford cyclopentenone **74** (18.4 mg, 70%) (56% yield over 2 steps) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.30 (m, 2H), 7.31 – 7.24 (m, 3H), 7.21 – 7.16 (m, 3H), 7.14 – 7.08 (m, 7H), 6.16 (s, 1H), 4.65 (d, *J* = 10.3 Hz, 1H), 4.42 (d, *J* = 10.3 Hz, 1H), 4.33 (s, 1H), 4.10 (d, *J* = 12.4 Hz, 1H), 3.93 (d, *J* = 12.4 Hz, 1H), 3.62 (d, *J* = 2.7 Hz, 1H), 1.85 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.3, 179.1, 141.0, 137.0, 136.5, 130.7, 130.0, 129.3, 129.3, 128.4, 128.2, 128.1, 128.1, 127.6, 127.4, 76.5, 76.5, 60.8, 51.4, 18.2 ppm; **IR** (thin film) 3405, 3063, 3030, 2924, 2857, 1953, 1880, 1810, 1711, 1623 cm^{-1}; **MS** (ESI) *m/z* 406.1795 (406.1783 calcd for $C_{26}H_{25}NNaO_2^+$ $[MNa]^+$).



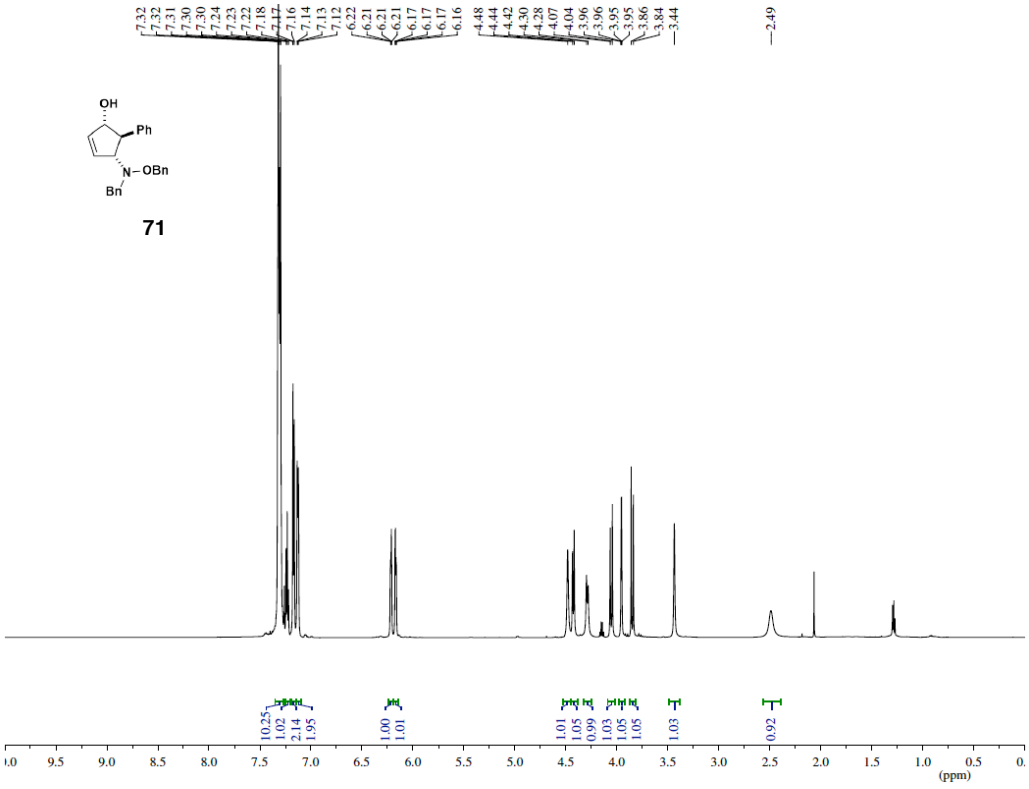
3-(benzyl(benzyloxy)amino)-2-phenylcyclopentan-1-one (75): A solution of **38** (20.0 mg, 0.054 mmol) in 5 mL dry THF is cycled between N_2 and vacuum (5x) before addition of Pd/C (10 wt%) (1.1 mg, 0.0011 mmol). The reaction is then placed under an atmosphere of H_2 by cycling between vacuum and H_2 (5x) and stirred at rt. When no more starting material was observed by TLC, the reaction was filtered through Celite, washing with EtOAc. Once

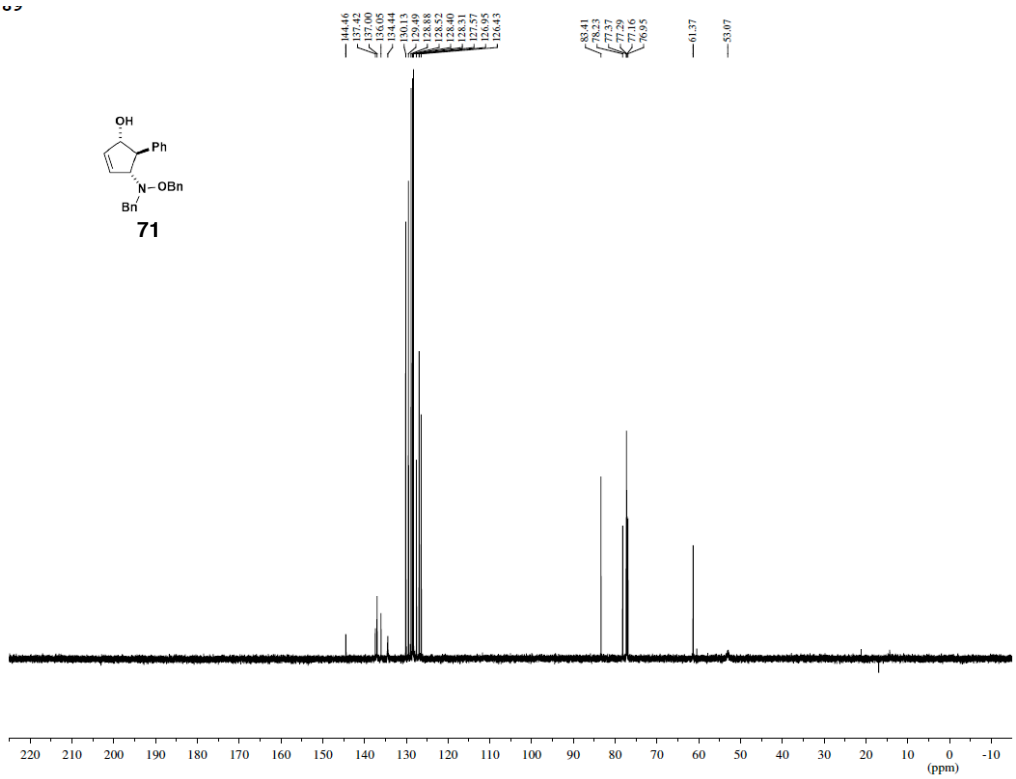
the solvent was removed, the residue was purified by flash column chromatography to give **75** (20.1 mg, quant.). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 11H), 7.15 (dd, *J* = 7.2, 1.7 Hz, 2H), 7.02 (dd, *J* = 6.3, 3.0 Hz, 2H), 4.40 (d, *J* = 10.3 Hz, 1H), 3.89 (d, *J* = 13.0 Hz, 1H), 3.85 (d, *J* = 12.9 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.72 (d, *J* = 9.5 Hz, 1H), 2.63 – 2.54 (m, 1H), 2.37 – 2.30 (m, 2H), 2.30 – 2.20 (m, 1H) ppm.

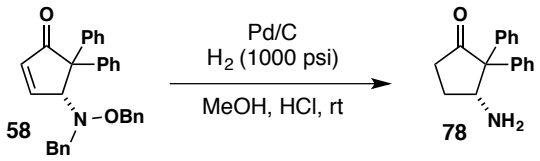


4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-ol (71 and **72):** 4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-one (**38**) (231 mg, 0.63 mmol) and $YbCl_3·6H_2O$ (387.5 mg, 1.25 mmol) was dissolved in 3 mL THF, then 23 mL MeOH was added and the solution stirred while cooling to -78 ºC. $NaBH_4$ (47.3 mg, 1.25 mmol) was added in one portion and the reaction was stirred at -78 ºC until complete (1 h) as determined by thin layer chromatography (2:1 hexanes:ethyl acetate, stained with anisaldehyde). The reaction was then quenched with saturated aqueous NH_4Cl (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue (20:1 dr as determined by ^{1}H NMR of crude mixture) was purified by flash column chromatography to afford cyclopentenone **71** (174 mg, 78%) as a colorless oil. *Major Diastereomer:* **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 10H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.15 – 7.09 (m, 2H), 6.24 – 6.19 (m, 1H), 6.19 – 6.14 (m, 1H), 4.48 (s, 1H), 4.43 (d, *J* = 9.8 Hz, 1H), 4.29 (d, *J* = 9.8 Hz, 1H), 4.06 (d, *J* = 12.7 Hz, 1H), 3.96 (q, *J* = 2.1 Hz, 1H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.44 (s, 1H), 2.49 (s, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 144.5,

137.4, 137.0, 136.1, 134.4, 130.1, 129.5, 128.9, 128.5, 128.4, 128.3, 127.6, 127.0, 126.4, 83.4, 78.2, 77.3, 61.4, 53.1 ppm; **IR** (thin film) 3414, 3062, 3030, 2878, 1602, 1495, 1454 cm^{-1}; **MS** (ESI) *m/z* 394.1785 (394.1783 calcd for $C_{25}H_{25}NNaO_2^+$ $[MNa]^+$). *Minor Diastereomer:* **^{1}H NMR** (600 MHz, Chloroform-d) δ 7.37 – 7.31 (m, 2H), 7.32 – 7.21 (m, 12H), 7.03 (s, 2H), 6.31 (d, J = 6.4 Hz, 1H), 6.12 (d, J = 5.8 Hz, 1H), 4.96 (d, J = 6.8 Hz, 1H), 4.49 – 4.40 (m, 1H), 4.40 – 4.24 (m, 2H), 3.89 (d, J = 12.9 Hz, 1H), 3.82 – 3.71 (m, 2H). ppm; **^{13}C** NMR (150 MHz, Chloroform-d) δ 139.0, 137.0, 135.8, 135.4, 130.0, 129.4, 129.1, 128.8, 128.3, 128.2, 128.0, 127.4, 127.1, 77.7, 77.0, 76.5, 61.6 ppm; **IR** (thin film) 3413, 3062, 3003, 2919, 1602, 1495, 1454, 1361 cm^{-1}; **MS** (ESI) *m/z* 394.1769 (394.1783 calcd for $C_{25}H_{25}NNaO_2^+$ $[MNa]^+$).

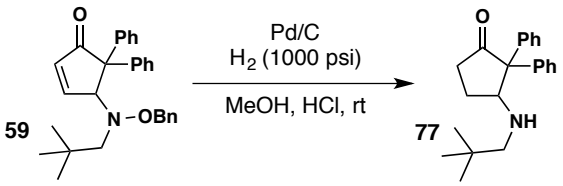






3-Amino-2,2-diphenylcyclopentan-1-one (78): In a 20 mL vial, 4-(benzyl(benzyloxy)amino)-5,5-diphenylcyclopent-2-en-1-one **58** (13.4 mg, 0.0301 mmol) was dissolved in MeOH (1.5 mL), followed by addition of Palladium on carbon (10 wt%) (1.6 mg, 0.0015 mmol). One drop of 12M HCl from an 18 gauge needle was added prior to placing the vial into the pressure vessel. The reaction mixture was placed under H_2 gas at 70 bar for 48h. The reaction mixture was filtered over Celite. The Celite pad was rinsed with ethyl acetate (3 x 5mL). The organic layer was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 5 ml). The combined organic layers were dried with Na_2SO_4, filtered and then concentrated *in vacuo* to afford **78** (7.6 mg,

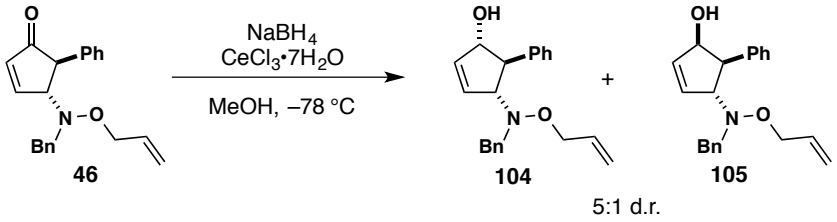
quantitative yield) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.6 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.29 – 7.24 (m, 3H), 7.24 – 7.19 (m, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.37 (t, *J* = 4.5 Hz, 1H), 2.75 – 2.60 (m, 1H), 2.46 – 2.29 (m, 2H), 1.83 – 1.74 (m, 1H), 1.69 (bs, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 216.3, 140.5, 139.8, 129.7, 128.8, 128.6, 128.2, 127.3, 127.0, 66.7, 56.4, 36.0, 27.5 ppm; **IR** (thin film) 3372, 3302, 3086, 3057, 3032, 2925, 2855, 1763, 1672 cm^{-1}; **MS** (EI) *m/z* 251.1305 (251.1310 calcd for $C_{17}H_{17}NO^+$ $[M]^+$).



3-(Neopentylamino)-2,2-diphenylcyclopentan-1-one (77): In a 20 mL vial, 4-((benzyloxy)(neopentyl)amino)-5,5-diphenylcyclopent-2-en-1-one **59** (41.5 mg, 0.098 mmol) was dissolved in MeOH (1.5 mL), followed by addition of Palladium on carbon (10 wt%) (5.2 mg, 0.0049 mmol). One drop of 12M HCl from an 18 gauge needle was added prior to placing the vial into the pressure vessel. The reaction mixture was placed under H_2 gas at 70 bar for 48h. The reaction mixture was filtered over Celite. The Celite pad was rinsed with ethyl acetate (3 x 5mL). The organic layer was then quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and then concentrated *in vacuo* to afford **77** (31.3 mg, quantitative yield) as a brown oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.28 – 7.21 (m, 3H), 7.20 (d, *J* = 7.5 Hz, 3H), 3.94 (t, *J* = 4.3 Hz, 1H), 2.63 (ddd, *J* = 18.9, 9.0, 7.2 Hz, 1H), 2.46 (d, *J* = 11.1 Hz, 1H), 2.28 (ddd, *J* = 18.8, 9.1, 4.5 Hz, 1H), 2.22 (d, *J* = 11.0 Hz, 1H), 2.19 (dddd, *J* = 11.5, 9.1, 5.9, 3.5 Hz, 1H), 1.89 (dddd, *J* = 13.4, 9.1, 4.4, 4.4 Hz, 1H), 1.29 (s, 1H), 0.76 (s, 9H) ppm; **^{13}C NMR** (150 MHz,

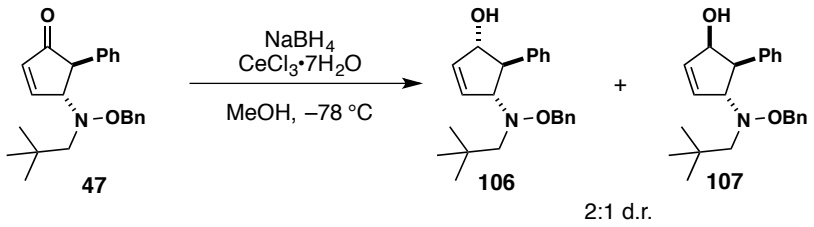
$CDCl_3$) δ 216.6, 140.4, 140.0, 66.3, 63.4, 59.8, 35.5, 31.7, 29.8, 27.7, 23.8 ppm; **IR** (thin film) 3347, 3087, 3058, 3031, 2951, 2864, 1737, 1599 cm^{-1}; **MS** (EI) *m/z* 321.2096 (321.2093 calcd for $C_{22}H_{27}NO^+$ $[M]^+$).

Synthesis of Allylic Alcohols:



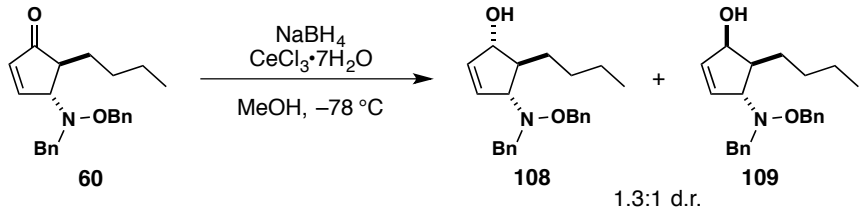
4-((Allyloxy)(benzyl)amino)-5-phenylcyclopent-2-en-1-ol (104): A solution of **46** (300.0 mg, 0.94 mmol) in MeOH (22 mL) was treated with $CeCl_3$•$7H_2O$ (384.9 mg, 1.03 mmol) and stirred at rt for 20 min. The solution was cooled to –78 °C and subsequently treated with $NaBH_4$ (46.2 mg, 1.22 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with H_2O, and allowed to come to rt before removal of the solvent and extracting with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 5:1 mixture of diastereomers. The residue was purified by flash column chromatography to afford the separated allylic alcohols **104** and **105** (286.8 mg, 95% combined yield) as yellow oils. *Major diastereomer*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.27 – 7.24 (m, 5H), 7.25 – 7.18 (m, 1H), 7.18 – 7.13 (m, 2H), 6.19 (ddd, *J* = 5.7, 1.9, 1.9 Hz, 1H), 6.11 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.70 (dddd, *J* = 16.8, 10.3, 6.3, 6.3 Hz, 1H), 5.17 – 5.08 (m, 1H), 5.13–5.11 (m, 1H), 4.48 (d, *J* = 6.1 Hz, 1H), 4.04 (d, *J* = 12.7 Hz, 1H), 3.96 – 3.90 (m, 1H), 3.90 – 3.83 (m, 2H), 3.81 (d, *J* = 12.8 Hz, 1H), 3.43 (s, 1H), 2.65 (s, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.4, 137.3, 137.1, 134.4, 133.0, 130.0, 128.9, 128.3, 127.5, 127.0, 126.5, 119.0, 83.3, 78.0, 76.0, 61.4,

53.3 ppm; **IR** (thin film) 3413, 3061, 3029, 2918, 2851, 1601, 1494, 1453, 1344, 1080, 1027, 995, 925 cm^{-1}; **MS** (ESI) *m/z* 344.1605 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$). *Minor diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.29 – 7.18 (m, 8H), 6.27 (d, *J* = 4.3 Hz, 1H), 6.11 – 6.05 (m, 1H), 5.63 (dddd, *J* = 16.7, 10.4, 6.3, 6.3 Hz, 1H), 5.07 – 5.00 (m, 2H), 4.92 (d, *J* = 5.9 Hz, 1H), 4.40 – 4.36 (m, 1H), 3.90 – 3.82 (m, 3H), 3.76 – 3.68 (m, 2H), 1.25 (d, *J* = 12.8 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CHCl_3$) δ 139.0, 137.7, 135.9, 135.2, 133.8, 129.8, 129.4, 128.8, 128.2, 127.4, 127.1, 117.9, 77.6, 76.2, 75.9, 61.6, 50.8 ppm; **IR** (thin film) 3425, 3061, 3029, 2917, 2865, 1602, 1494, 1453, 1342, 1069, 1029, 994 $^{-1}$; **MS** (ESI) *m/z* 344.1636 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$).



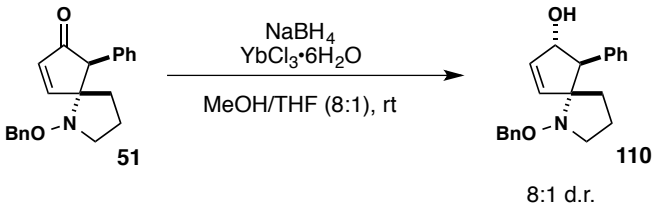
4-((Benzyloxy)(neopentyl)amino)-5-phenylcyclopent-2-en-1-ol (106 and **107):** A solution of **47** (52.6 mg, 0.15 mmol) in MeOH (3.6 mL) was treated with $CeCl_3$•$7H_2O$ (61.7 mg, 0.17 mmol) and stirred at rt for 20 min. The solution was cooled to –78 °C and subsequently treated with $NaBH_4$ (7.4 mg, 0.20 mmol) and stirred at this temperature until the reaction was complete as judged by TLC. The reaction was quenched with H_2O and allowed to come to rt before extracting with EtOAc (3x 6 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 2:1 mixture of diastereomers. The residue was purified by flash column chromatography to afford the separated allylic alcohols **106** and **107** (37.1 mg, 70% combined yield) as yellow oils. *Major diastereomer*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 5H), 7.23 – 7.19 (m, 3H), 7.16 – 7.11 (m, 2H), 6.18 (dd, *J* =

5.7, 2.1 Hz, 1H), 6.15 (ddd, *J* = 5.7, 1.8, 1.8 Hz, 1H), 4.76 (d, *J* = 10.0 Hz, 1H), 4.58 (d, *J* = 9.9 Hz, 1H), 4.45 (s, 1H), 3.95 (s, 1H), 3.25 (dd, *J* = 2.6, 2.6 Hz, 1H), 2.82 (d, *J* = 14.1 Hz, 1H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.33 (s, 1H), 0.95 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 144.9, 136.7, 136.2, 134.6, 129.1, 128.9, 128.6, 128.3, 127.0, 126.3, 83.3, 80.9, 75.6, 69.0, 53.9, 31.7, 28.7 ppm; **IR** (thin film) 3408, 3086, 3061, 3029, 2951, 2903, 2866, 1945, 1804, 1602, 1453, 1360, 1209, 1020, 1011, 909 cm^{-1}; **MS** (ESI) *m/z* 374.2069 (374.2096 calcd for $C_{23}H_{29}NNaO_2^+$ $[MNa]^+$). *Minor Diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.30 – 7.24 (m, 6H), 7.14 (d, *J* = 6.0 Hz, 2H), 6.30 (d, *J* = 5.6 Hz, 1H), 6.13 – 6.04 (m, 1H), 4.92 (d, *J* = 6.5 Hz, 1H), 4.66 – 4.60 (m, 2H), 4.56 (s, 1H), 3.53 (dd, *J* = 6.2 Hz, 1H), 2.61 (d, *J* = 14.2 Hz, 1H), 2.48 (d, *J* = 14.2 Hz, 1H), 1.25 (s, 1H), 0.89 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.3, 137.2, 136.1, 135.5, 129.4, 128.8, 128.6, 128.4, 127.9, 127.0, 78.4, 77.4, 74.8, 67.6, 50.4, 31.6, 28.6 ppm; **IR** (thin film) 3412, 3086, 3061, 3030, 2951, 2904, 2865, 1947, 1807, 1602, 1453, 1361, 1208, 1027, 910 cm^{-1}; **MS** (ESI) *m/z* 374.2097 (374.2096 calcd for $C_{23}H_{29}NNaO_2^+$ $[MNa]^+$).



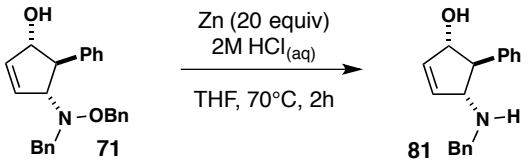
4-(Benzyl(benzyloxy)amino)-5-butylcyclopent-2-en-1-ol (108 and **109):** A solution of **60** (145.5 mg, 0.42 mmol) in MeOH (10 mL) was treated with $CeCl_3$•$7H_2O$ (170.6 mg, 0.45 mmol) and stirred at rt for 20 min. The solution was cooled to –30 °C and subsequently treated with $NaBH_4$ (20.5 mg, 0.54 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with H_2O and allowed to come to rt before extracting with EtOAc (3x 10 mL). The combined organic phases were dried over

$MgSO_4$, filtered and then concentrated *in vacuo*. ^{1}H NMR analysis of the crude reaction mixture indicated a 1.3:1 mixture of diastereomers. The residue was purified by flash column chromatography to afford the separated allylic alcohols **108** and **109** (132.6 mg, 90% combined yield) as a yellow oil (major) and light orange solid (minor). *Major diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 5.9 Hz, 3H), 7.08 – 7.05 (m, 2H), 6.03 (d, *J* = 5.3 Hz, 1H), 5.99 – 5.95 (m, 1H), 4.35 (d, *J* = 9.7 Hz, 1H), 4.24 – 4.18 (m, 1H), 4.15 (d, *J* = 8.4 Hz, 1H), 3.96 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.51 (s, 1H), 2.28 (s, 1H), 2.15 (s, 1H), 1.42 – 1.27 (m, 6H), 0.90 (dd, *J* = 7.0, 7.0 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 137.9, 136.7, 136.1, 133.0, 130.0, 129.5, 128.5, 128.4, 128.3, 127.6, 80.9, 77.2, 76.1, 61.3, 46.9, 33.6, 30.1, 23.0, 14.2 ppm; **IR** (thin film) 3422, 3087, 3062, 3031, 2955, 2926, 2856, 1496, 1454, 1359, 1209, 1028, 1000 cm^{-1}; **MS** (ESI) *m/z* 374.2101 (374.2096 calcd for $C_{23}H_{29}NNaO_2$ $[MNa]^+$). *Minor Diastereomer*: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.11 – 7.02 (m, 2H), 6.24 (d, *J* = 5.2 Hz, 1H), 6.06 (ddd, *J* = 5.8, 2.1, 2.1 Hz, 1H), 4.78 (d, *J* = 5.6 Hz, 1H), 4.34 (s, 2H), 3.93 (d, *J* = 13.0 Hz, 1H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.80 (s, 1H), 2.13 (dddd, *J* = 12.5, 6.1, 6.1, 6.1 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.52 – 1.45 (m, 1H), 1.45 – 1.38 (m, 1H), 1.37 – 1.28 (m, 3H), 1.14 (s, 1H), 0.91 (dd, *J* = 7.1, 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3, 137.2, 136.0, 134.7, 129.8, 129.1, 128.3, 127.9, 127.4, 76.7, 76.2, 76.1, 60.3, 44.6, 31.0, 27.5, 23.2, 14.3 ppm; **IR** (thin film) 3376, 3089, 3064, 3033, 2956, 2930, 2872, 2859, 1606, 1496, 1454, 1362, 1265, 1210, 1028, 906 cm^{-1}; **MS** (ESI) *m/z* 374.2087 (374.2096 calcd for $C_{23}H_{29}NNaO_2$ $[MNa]^+$).

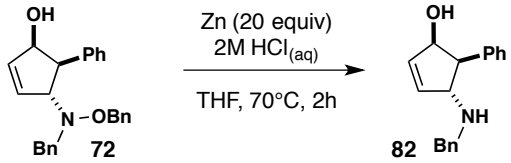


1-(Benzyloxy)-6-phenyl-1-azaspiro[4.4]non-8-en-7-ol (110): A solution of **51** (85.0 mg, 0.27 mmol) in MeOH (3.6 mL) and THF (0.4 mL) was treated with $YbCl_3 \bullet 6H_2O$ (206.4 mg, 0.53 mmol) and stirred at rt for 20 min. The solution was subsequently treated with $NaBH_4$ (20.1 mg, 0.53 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with saturated NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford allylic alcohol **110** (66.5 mg, 77%, isolated as an inseparable mixture of diastereomers with 8:1 dr) as a light yellow oil. *Major*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39 – 7.28 (m, 8H), 7.27 – 7.22 (m, 2H), 6.18 (dd, *J* = 5.7, 1.9 Hz, 1H), 6.02 (d, *J* = 5.3 Hz, 1H), 5.19 (dd, *J* = 6.3, 6.3 Hz, 1H), 4.80 – 4.67 (m, 2H), 3.68 (d, *J* = 7.0 Hz, 1H), 3.17 – 2.99 (m, 2H), 1.70 – 1.60 (m, 2H), 1.59 – 1.49 (m, 1H), 1.49 – 1.38 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ138.2, 137.9, 137.6, 137.2, 130.6, 128.9, 128.5, 128.4, 127.9, 127.1, 83.0, 78.3, 76.6, 54.7, 53.3, 30.6, 19.3 ppm; **IR** (thin film) 3413, 3086, 3059, 3029, 2940, 2866, 1601, 1494, 1453, 1362, 1208, 1080, 1026, 974 cm^{-1}; **MS** (ESI) *m/z* 344.1640 (344.1626 calcd for $C_{21}H_{23}NNaO_2$ $[MNa]^+$).

Reductive N–O bond cleavage:

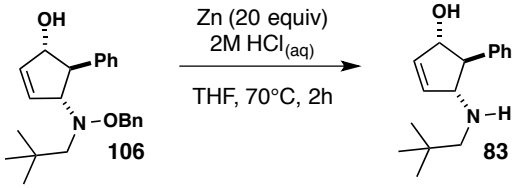


4-(Benzylamino)-5-phenylcyclopent-2-en-1-ol (81): 4-(Benzyl(benzyloxy)amino)-5-phenylcyclopent-2-en-1-ol **71** (13.3 mg, 0.036 mmol) was dissolved in 0.5 mL THF, followed by addition of 6-9 micron Zn powder (46.8 mg, 0.716 mmol). Next, 2M HCl (1 mL) in H_2O was added and the solution was heated to 70 ºC. Reaction was stirred until complete (2 h) as determined by thin layer chromatography. The reaction was then quenched by the addition of 4M $NaOH_{(aq)}$ until pH 14 was reached and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography (3% MeOH in CH_2Cl_2) to afford the free amine **81** (9.5 mg, quantitative yield) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.5 Hz, 2H), 7.28 – 7.22 (m, 4H), 7.19 (t, *J* = 7.2 Hz, 4H), 6.00 (t, *J* = 7.0 Hz, 2H), 4.64 (d, *J* = 4.5 Hz, 1H), 3.84 – 3.77 (m, 2H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.18 (s, 2H), 3.00 (t, *J* = 4.9 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 143.0, 138.9, 135.6, 134.5, 128.9, 128.6, 127.6, 127.4, 126.8, 83.9, 69.6, 62.0, 51.3 ppm; **IR** (thin film) 3294, 3061, 3028, 2922, 2854, 1951, 1877, 1810, 1734, 1602, 1495 cm^{-1}; **MS** (ESI) *m/z* 288.1371 (288.1371 calcd for $C_{18}H_{19}NNaO^+$ $[MNa]^+$).



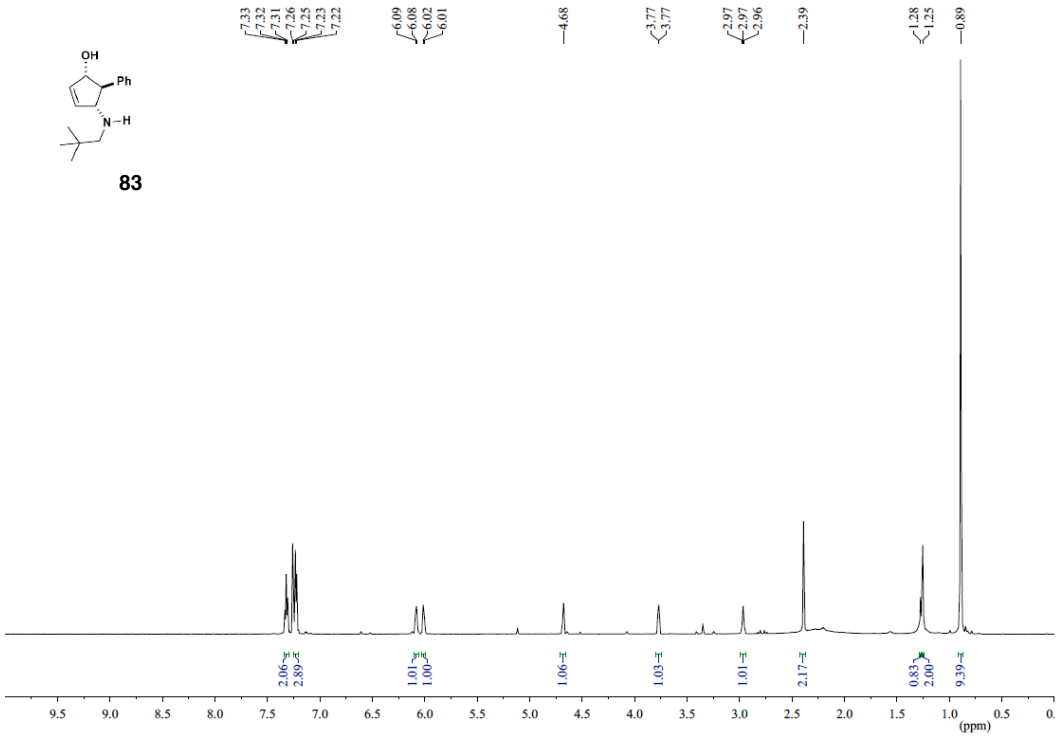
4-(Benzylamino)-5-phenylcyclopent-2-en-1-ol (82): A solution of **72** (20.0 mg, 0.062 mmol) in THF (1.9 mL) was treated with Zn (81.4 mg, 1.2 mmol), followed by slow addition of 3.7 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred until no starting material was observed by TLC. The reaction was then cooled to rt, quenched

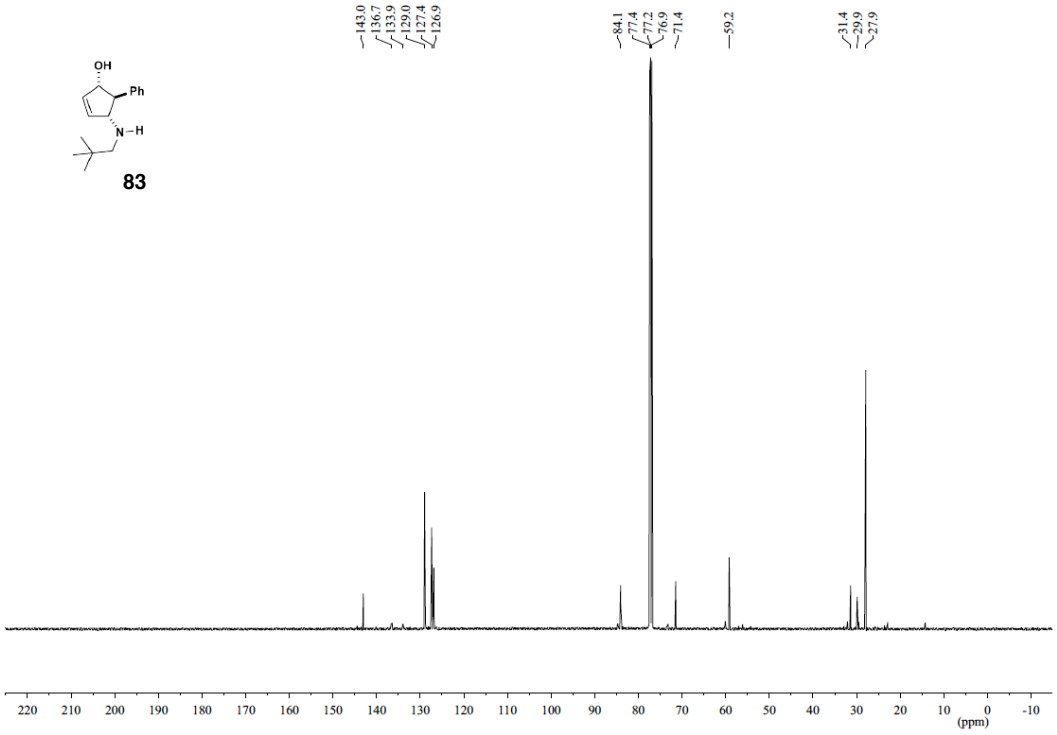
with saturated $NaHCO_3$, then the pH was adjusted to 9 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **82** (11.7 mg, 98%) as a light yellow solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.32 (m, 2H), 7.31 – 7.27 (m, 3H), 7.27 – 7.24 (m, 2H), 7.24 – 7.18 (m, 3H), 6.21 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.04 (ddd, *J* = 5.8, 2.2, 2.2 Hz, 1H), 4.84 (ddd, *J* = 6.3, 2.1, 2.1 Hz, 1H), 4.31 (dddd, *J* = 6.6, 1.8, 1.8, 1.8 Hz, 1H), 3.77 (s, 2H), 3.23 (dd, *J* = 6.4, 6.4 Hz, 1H), 1.57 (s, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.1, 138.7, 138.2, 133.2, 129.4, 128.8, 128.5, 128.3, 127.2, 127.2, 77.3, 67.2, 57.8, 52.4 ppm; **IR** (thin film) 3302, 3059, 3027, 2901, 2851, 1601, 1553, 1493, 1453, 1319, 1094, 1070, 1028 cm^{-1}; **MS** (ESI) *m/z* 288.1354 (288.1364 calcd for $C_{18}H_{19}NNaO$ $[MNa]^+$).

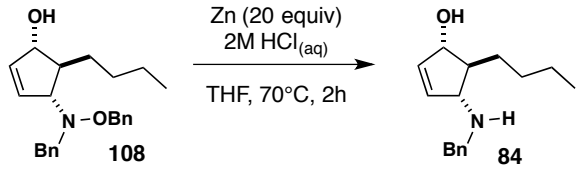


4-(Neopentylamino)-5-phenylcyclopent-2-en-1-ol (83): A solution of **106** (7.6 mg, 0.022 mmol) in THF (0.7 mL) was treated with Zn (28.3 mg, 0.43 mmol), followed by slow addition of 1.3 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred until no starting material was observed by TLC. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **83** (3.1 mg, 58%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.32 (t, *J* = 7.3 Hz, 2H), 7.27 – 7.20 (m, 3H), 6.08 (d, *J* = 5.7 Hz, 1H), 6.01 (d, *J* = 5.2 Hz, 1H), 4.68 (s, 1H),

3.80 – 3.75 (m, 1H), 2.99 – 2.94 (m, 1H), 2.39 (s, 2H), 1.28 (s, 1H), 1.25 (s, 1H), 0.89 (s, 9H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.0, 136.7, 133.9, 129.0, 127.4, 126.9, 84.1, 71.4, 59.2, 31.4, 29.9, 27.9 ppm; **IR** (thin film) 3293, 3061, 3028, 2953, 2926, 2855, 1555, 1467, 1453, 1363, 1079, 1013, 906 cm^{-1}; **MS** (ESI) *m/z* 246.1853 (246.1858 calcd for $C_{16}H_{24}NO$ $[MH]^+$).

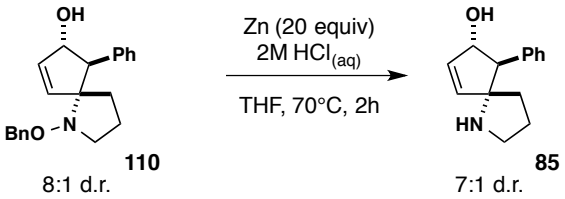






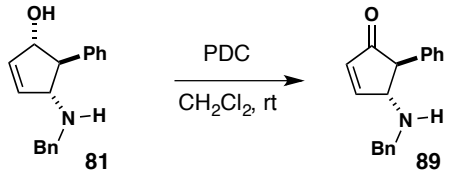
4-(Benzylamino)-5-butylcyclopent-2-en-1-ol (84): A solution of **108** (30.2 mg, 0.086 mmol) in THF (2.6 mL) was treated with Zn (112.4 mg, 1.7 mmol), followed by slow addition of 5.2 mL 2M HCl. The reaction was placed in an oil bath at 70 °C and stirred for 40 min, until no starting material was observed by TLC. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3 M NaOH before extraction with EtOAc (3 x 5 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **84** (17.3 mg, 82%) as a yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 5.97 – 5.91 (m, 1H), 5.89 (ddd, *J* = 5.7, 1.7, 1.7 Hz, 1H), 4.32 – 4.27 (m, 1H), 3.84 (d, *J* = 2.0 Hz, 2H), 3.34 – 3.28 (m, 1H), 2.53 (s, 2H),

1.79 (dddd, J = 10.0, 3.6, 3.6, 3.6 Hz, 1H), 1.56 – 1.28 (m, 6H), 0.91 (dd, J = 7.1, 7.1 Hz, 3H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 139.5, 135.7, 134.4, 128.6, 128.5, 127.4, 81.6, 67.9, 54.7, 51.8, 33.1, 30.1, 23.1, 14.2 ppm; **IR** (thin film) 3290, 3059, 2039, 2955, 2924, 2855, 1454, 1354, 1073, 1027, 996 cm^{-1}; **MS** (ESI) *m/z* 268.1662 (268.1677 calcd for $C_{16}H_{23}NNaO$ $[MNa]^+$).

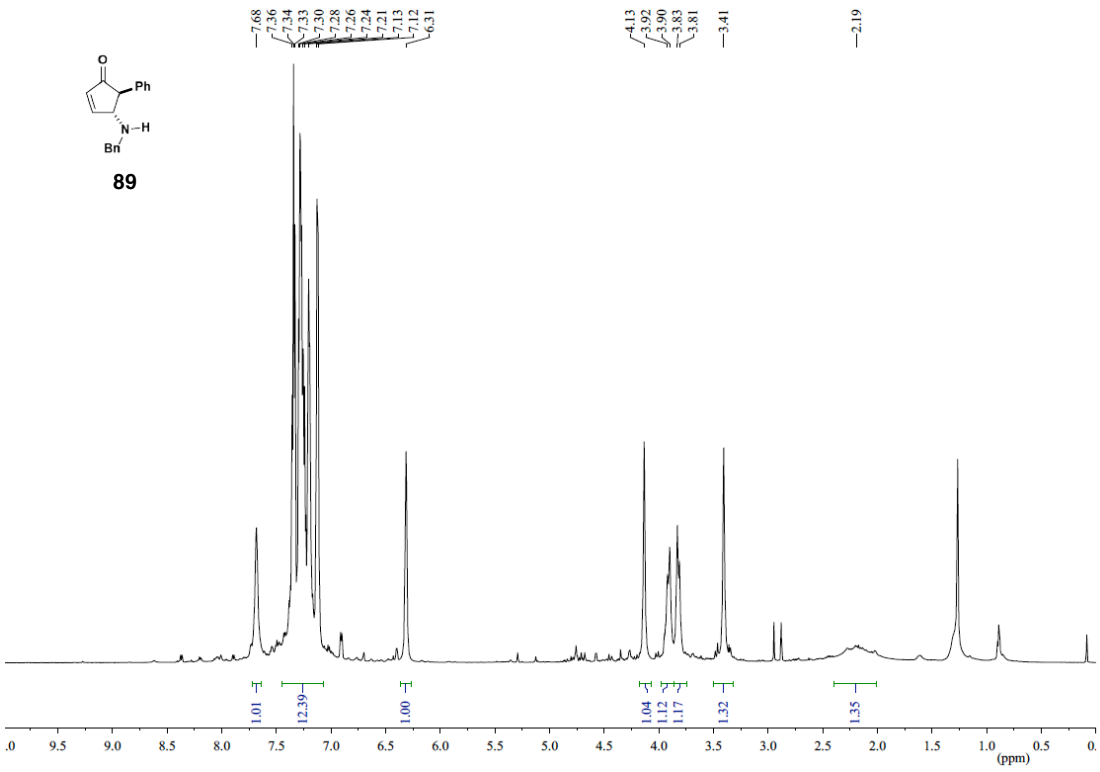


6-Phenyl-1-azaspiro[4.4]non-8-en-7-ol (85): A solution of (**110**) (66.5 mg, 0.21 mmol, as an 8:1 mixture of diastereomers) in 6.4 mL THF was treated with zinc (274.7 mg, 4.2 mmol), followed by dropwise addition of 2M HCl (12.7 mL). The reaction was placed in an oil bath heated to 70 °C and stirred for 2 hours. The reaction was then cooled to rt, quenched with saturated $NaHCO_3$, then the pH was adjusted to ~10 using 3M NaOH before extraction with EtOAc (3 x 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and solvent removed *in vacuo*. The residue was purified by flash column chromatography to afford **85** (34.3 mg, 77%) as a yellow oil and an inseparable 7:1 mixture of diastereomers. *Major*: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.32 – 7.23 (m, 5H), 6.04 (d, J = 5.8 Hz, 1H), 6.01 (dd, J = 5.8, 1.9 Hz, 1H), 5.13 (ddd, J = 6.4, 1.6, 1.6 Hz, 1H), 3.37 (d, J = 6.4 Hz, 1H), 2.94 (ddd, J = 10.4, 7.9, 5.0 Hz, 1H), 2.84 (ddd, J = 10.6, 6.8, 6.8 Hz, 1H), 2.14 (bs, 3H), 1.73 – 1.46 (m, 5H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 140.6, 138.0, 134.7, 130.7, 128.4, 127.2, 77.7, 76.6, 61.0, 45.7, 34.8, 25.7 ppm; **IR** (thin film) 3363, 3060, 3029, 2922, 2852, 1600, 1554, 1455, 1387, 1104, 1083, 1033 cm^{-1}; **MS** (ESI) *m/z* 216.1393 (216.1388 calcd for $C_{14}H_{18}NO$ $[MH]^+$).

Allylic Oxidation:



4-(Benzylamino)-5-phenylcyclopent-2-en-1-one (89): A solution of **81** (50.0 mg, 0.19 mmol) in 1.9 mL dry DMF was treated with pyridinium dichromate (PDC) (354 mg, 0.94 mmol) and stir ed at rt for 2 h. The reaction was quenched with water (20 mL) and diluted with EtOAc (5 mL). The phases were separated, and the aqueous phase extracted with EtOAc (3 x 5 mL). Subsequently, the combined organic phases were washed with H_2O (5 x 5 mL) and brine (2 x 5 mL). The organic layer was dried over $MgSO_4$, filtered and solvent removed *in vacuo* to give the crude, desired product **89** (35 mg, 70%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.42 – 7.03 (m, 10H), 6.31 (s, 1H), 4.13 (s, 1H), 3.91 (d, J = 12.8 Hz, 1H), 3.82 (d, J = 12.3 Hz, 1H), 3.41 (s, 1H), 2.19 (bs, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.1, 163.3, 139.4, 138.4, 134.0, 129.0, 128.6, 128.3, 127.4, 127.3, 67.3, 60.6, 51.9 ppm; **IR** (thin film) 3085, 3061, 3029, 2925, 2853, 1705, 1494, 1453, 1265 cm^{-1}; **MS** (ESI) *m/z* 264.1376 (264.1388 calcd for $C_{18}H_{18}NO$ $[MH]^+$).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7.33
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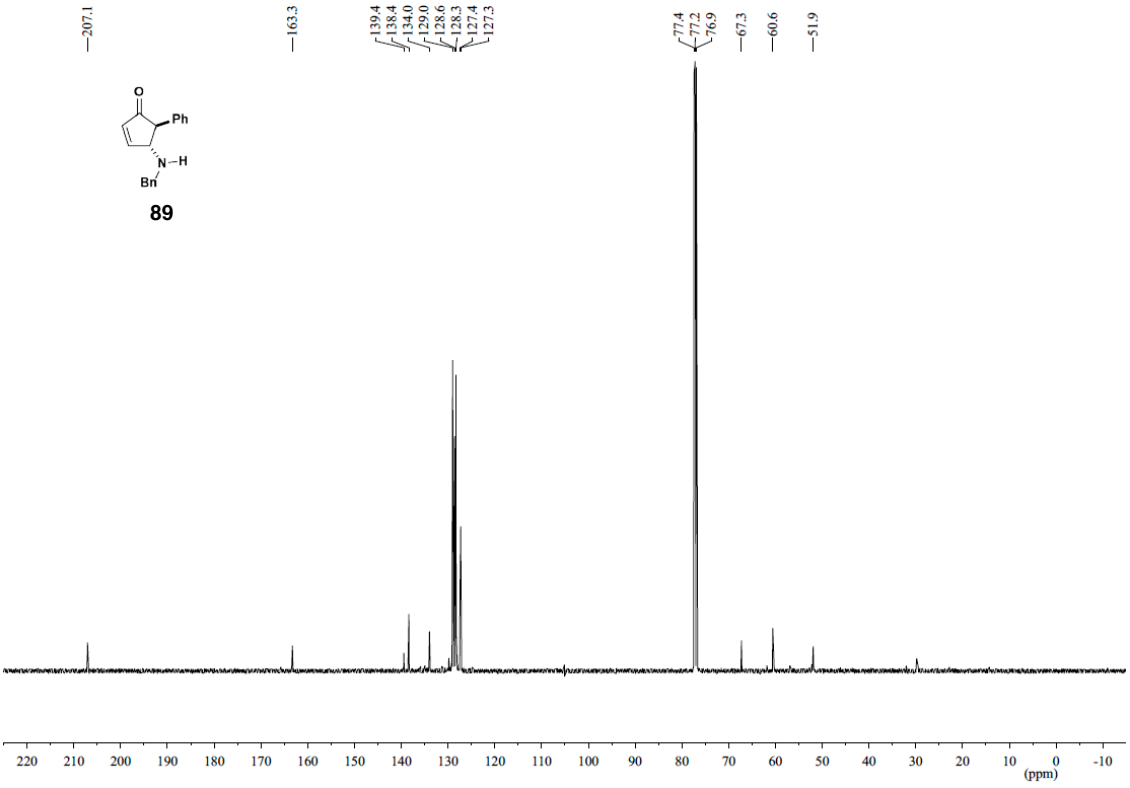
7.28
7.26
7.24
7.21
7.13
7.12
6.31
4.13
3.92
3.90
3.83
3.81
3.41
2.19
O
Ph
N–H
Bn
89
1.01
12.39
1.00
1.04
1.12
1.17
1.32
1.35
(ppm)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128.3
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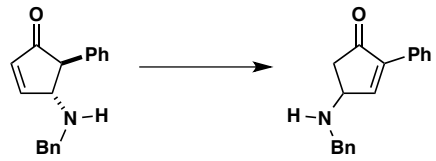
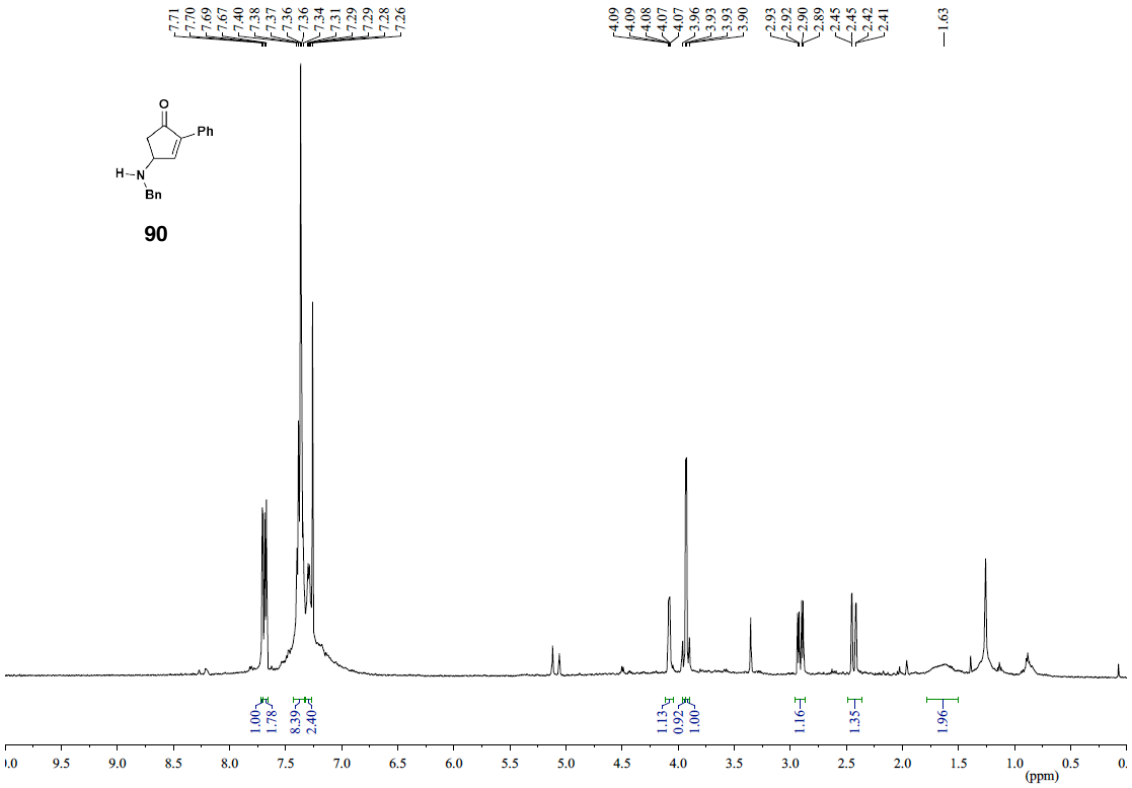
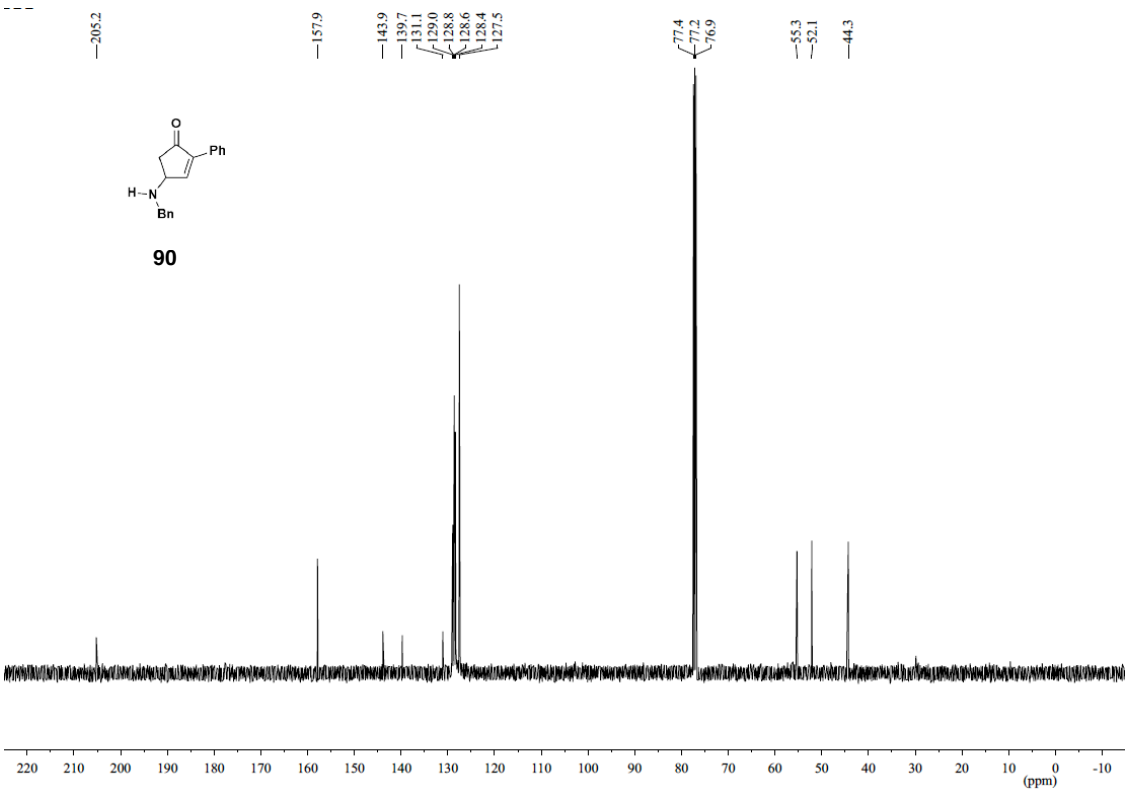
O
Ph
N–H
Bn
89
(ppm)



4-(Benzylamino)-2-phenylcyclopent-2-en-1-one (90): Upon purification on silica, exposure to base, or standing at rt, **89** isomerizes to the more thermodynamically stable cyclopentenone **90**. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 2.6 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.41 – 7.32 (m, 7H), 7.32 – 7.27 (m, 1H), 4.08 (ddd, *J* = 5.9, 2.5, 2.5 Hz, 1H), 3.95 (d, *J* = 13.0 Hz, 1H), 3.91 (d, *J* = 13.0 Hz, 1H), 2.91 (dd, *J* = 18.5, 6.2 Hz, 1H), 2.43 (dd, *J* = 18.5, 2.4 Hz, 1H), 1.63 (bs, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 205.2, 157.9, 143.9, 139.7, 131.1, 129.0, 128.8, 128.6, 128.4, 127.5, 55.3, 52.1, 44.3 ppm; **IR** (thin film) 3086, 3059, 3029, 2925, 2851, 1704, 1598, 1577, 1494, 1452, 1265 cm^{-1}; **MS** (ESI) *m/z* 264.1374 (264.1388 calcd for $C_{18}H_{18}NO$ $[MH]^+$).





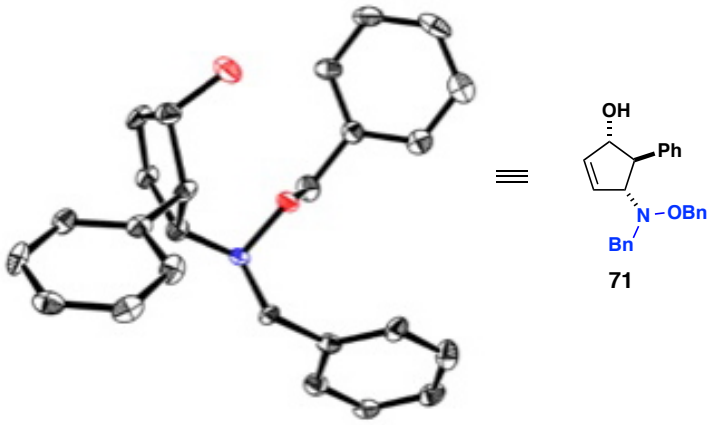
Crystallographic Experimental Section

A colorless crystal of approximate dimensions 0.3*0.1*0.1 mm was mounted on a glass fiber and transferred to a Bruker Kappa Apex II diffractometer. The APEX2 program was used to determine the unit cell parameters and data collection (15 sec / frame, 0.3 deg. /frame). The data were collected at 100K. The raw frame data were processed using APEX2 program. The absorption correction was applied using program SADABS. Subsequent calculations were carried out using SHELXTL program. The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. Hydrogen atomic positions were theoretically calculated. At convergence, wR2= 0.1517 and GOF = 0.957 for 274 variables refined against 4375 reflections, while R1= 0.0620 for 3625 reflections with $I>2\sigma(I)$. All ORTEP diagrams have been drawn with 50% probability ellipsoids.

Crystals were prepared by slow vapor diffusion using hexanes and ethyl acetate.

The crystal structure data can be obtained free of charge from the Cambridge Crystallographic Data Centre www.ccdc.cam.ac.uk/data_request/cif

Compound # 71 CCDC 986010



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5. A Mechanistic Investigation of the Aza-Piancatelli Rearrangement

5.1. Motivation for a Mechanistic Investigation

The Piancatelli rearrangement was developed in 1976,[39] but received limited attention from the synthetic community since then.[56,155] Despite the intriguing cascade mechanism of this transformation, there has been no detailed study on the mechanism of the reaction. Analysis has been limited to DeLera and co-workers' DFT calculations that verified the 4π conrotatory electrocyclization, and a similar report by Tantillo and Davis.[58,156] The challenges we encountered with developing an aza-Pianctelli rearrangement with non-aniline nucleophiles and a number of observations throughout our studies motivated us to investigate the cascade rearrangement from a fundamental mechanistic point of view. Our goals were to determine the role of the catalyst in the reaction, analyze the electronic effects of the aniline on reaction rates, and hopefully gain a more concrete understanding of the limitation to aniline nucleophiles.

5.2. Initial Observations and Investigations of Reaction Kinetics

Throughout the development of the aza-Piancatelli rearrangement with anilines, we noted that reaction times varied based on the aniline and furylcarbinol involved (see Chapter 2). However, during Dr. Leoni Palmer's investigations of the intramolecular aza-Piancatelli rearrangement for the formation of aza-spirocycles,[138] it became apparent that there was a clear dependence of rate on the electronic nature of the *para*-substituent on the aniline. In short, reactions with electron rich anilines were much slower compared to reactions with electron poor anilines.

Initially, we were interested in creating a Hammett plot to clearly map out the electronic effect of the substituents on the rate of the reaction. We began our studies by monitoring the

reaction of phenylfurylcarbinol (**1**) and *p*-iodoaniline (**2a**) by ^{1}H nuclear magnetic resonance (NMR) spectroscopy. The reaction was performed with $Sc(OTf)_3$ since $Dy(OTf)_3$ is paramagnetic and can interfere with accurate data collection. After collecting a baseline ^{1}H NMR spectrum of the furylcarbinol and aniline in MeCN-d3, the sample was ejected and $Sc(OTf)_3$ added. The sample was then re-inserted and spectra obtained every 117 seconds until the reaction was complete, as judged by lack of starting material. The NMR spectra collected allowed us to accurately map product appearance and starting material disappearance (Figure 5.1 A), and examining the first half of the reaction shows that there is a linear correlation of starting material disappearance and product appearance (Figure 5.1 B).

Following this initial result, we monitored the aza-Piancatelli rearrangement with other *para*-substituted anilines. Unfortunately it immediately became apparent that this method of data collection would not be universally applicable to the aza-Piancatelli rearrangement. Reactions with electron rich substrates, such as *p*-methoxyaniline, were extremely slow at room temperature (reactions did not go to completion over the course of 9 days) making it impractical collect spectra continually. At the same time, reactions with electron poor substitutents, such as *p*-cyanoaniline were so fast at room temperature, that data of the important initial phases of the reaction could not be collected. Since it was clear that this method would not result in accurate data for a Hammett plot, we ventured toward monitoring reaction progress by gas chromatography (GC). Data points were obtained by removing aliquots from the reaction mixture. Unfortunately we ran into issues with the chromatograph at our campus, and the undergraduate student working under my supervision, Jonathan Cook, was unable to get reliable data from this method.

In all, there were a multitude of issues with the methods presented above that were not ideal for a thorough mechanistic study. With regards to NMR experiments, we were not entirely pleased with the necessary switch to $Sc(OTf)_3$ since differences in the reaction compared to $Dy(OTf)_3$ might affect the interpretation of the results. Additionally, the logistics of running an NMR experiment necessitate removal of the sample from the magnet for addition of the catalyst. This results in lack of data over the first minute (or more) before data collection starts, and becomes problematic with fast reactions. Limitations in terms of the temperatures at which data can be collected made it difficult to collect data in slow reactions with electron-rich anilines, and finally the amount of time required for experiments on the departmental NMR machines proved to be taxing both financially and logistically.

With these factors considered, but a positive result with one substrate (Figure 5.1), we embarked on a quest to find a collaborator possessing the necessary laboratory facilities to obtain quality data, as well as experience with kinetic and mechanistic studies. Enter, Professor Jason Hein.

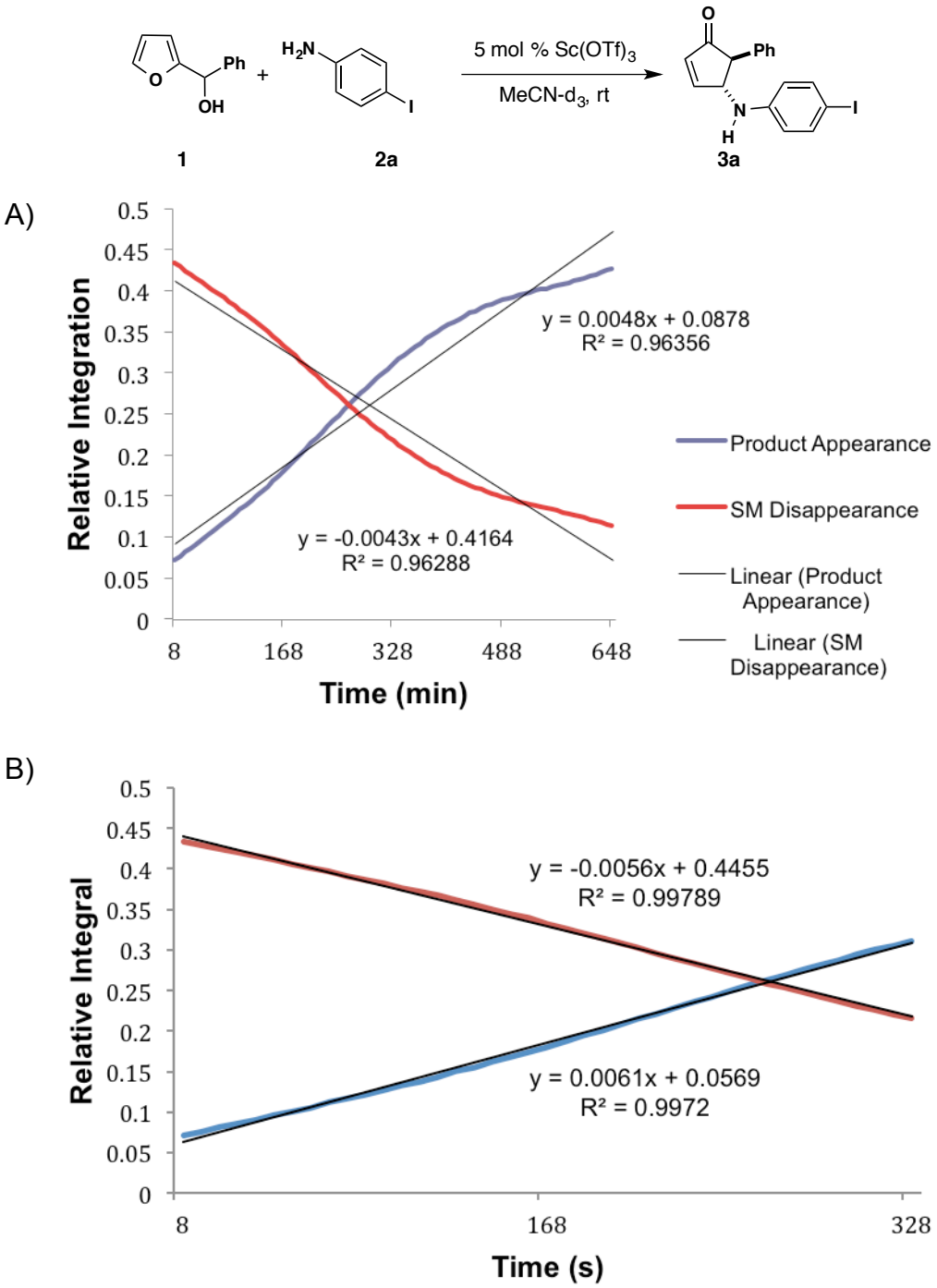


Figure 5.1. A) Graph of the reaction of furylcarbinol **1** and aniline **2a** monitored by ^{1}H NMR, and data collection over the course of 10 hours. B) Depiction of linear transformation over first half of reaction.

5.3. Mechanistic Investigations with the Hein Lab

In collaboration with the Hein Lab, we set out to investigate the aza-Piancatelli rearrangement with anilines to gain a kinetic and mechanistic understanding of the sequence of events leading up to the bond-forming electrocyclization.[157]

Our first forays into the mechanistic investigations started with kinetic experiments, modeled on our NMR studies, monitored by ReactIR with independent verification via HPLC/MS sampling throughout the reaction. We monitored the reaction of **1** and **2b** under $Dy(OTf)_3$ as well as TFA catalysis to ascertain if there were any rate differences. We chose TFA as our Brønsted acid because it is easier to handle and gives a cleaner reaction profile than triflic acid.

As discussed earlier in this thesis, it is known that metal triflates may release small amounts of triflic acid that can be responsible for catalysis.[158] Although we had performed control experiments during the development of the aza-Piancatelli rearrangement (Chapter 2, Table 2.1), we hoped to further support this finding during these mechanistic investigations by directly comparing the Lewis acid ($Dy(OTf)_3$) to the Brønsted acid (TFA) catalysis. The reaction progress was monitored as described and is depicted in Figure 5.2. It becomes immediately apparent that the reactions with Lewis ($Dy(OTf)_3$) and Brønsted acid (TFA) follow different reaction paths. We found that the reaction with $Dy(OTf)_3$ is zero-order in substrate and first-order in catalyst ([$Dy(OTf)_3$] = 2.0–12.0 mM) while the reaction with TFA is first order in both substrate and acid catalyst ([TFA] = 3.3–30.0 mM). This difference in reaction order confirms that *in situ* generation of triflic acid is not responsible for catalysis in the reaction with dysprosium.

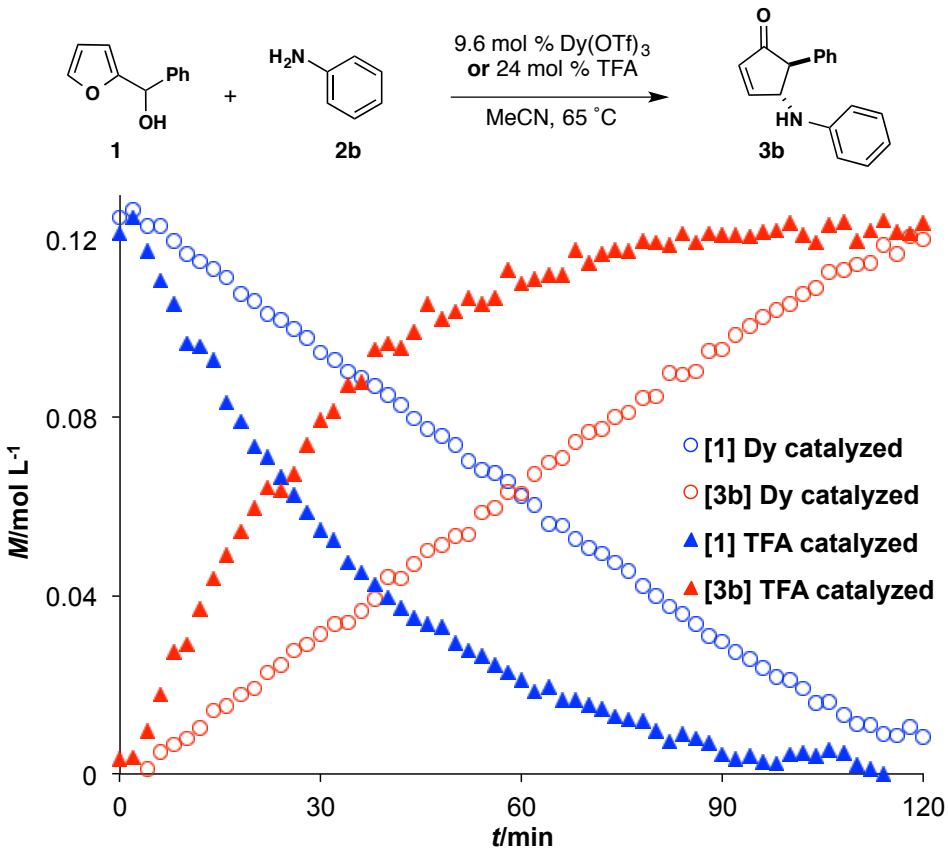


Figure 5.2. Reaction progress of $Dy(OTf)_3$ and TFA catalyzed rearrangement.

With the reaction order of the rearrangement established, our focus turned to the effect of the *p*-substituents on the aniline in the aza-Piancatelli rearrangement. In agreement with our empirical data, we found that the reaction rate increases when moving from electron donating substitutents (i.e. OMe) to electron withdrawing substituents (i.e. CO_2Me) (Figure 5.3). Interestingly, the Hammet ρ value for the $Dy(OTf)_3$ and TFA catalyzed processes are +3.36 and +3.30, respectively. This implies that the difference in reaction order is decoupled from the relative change in rate of the reaction.

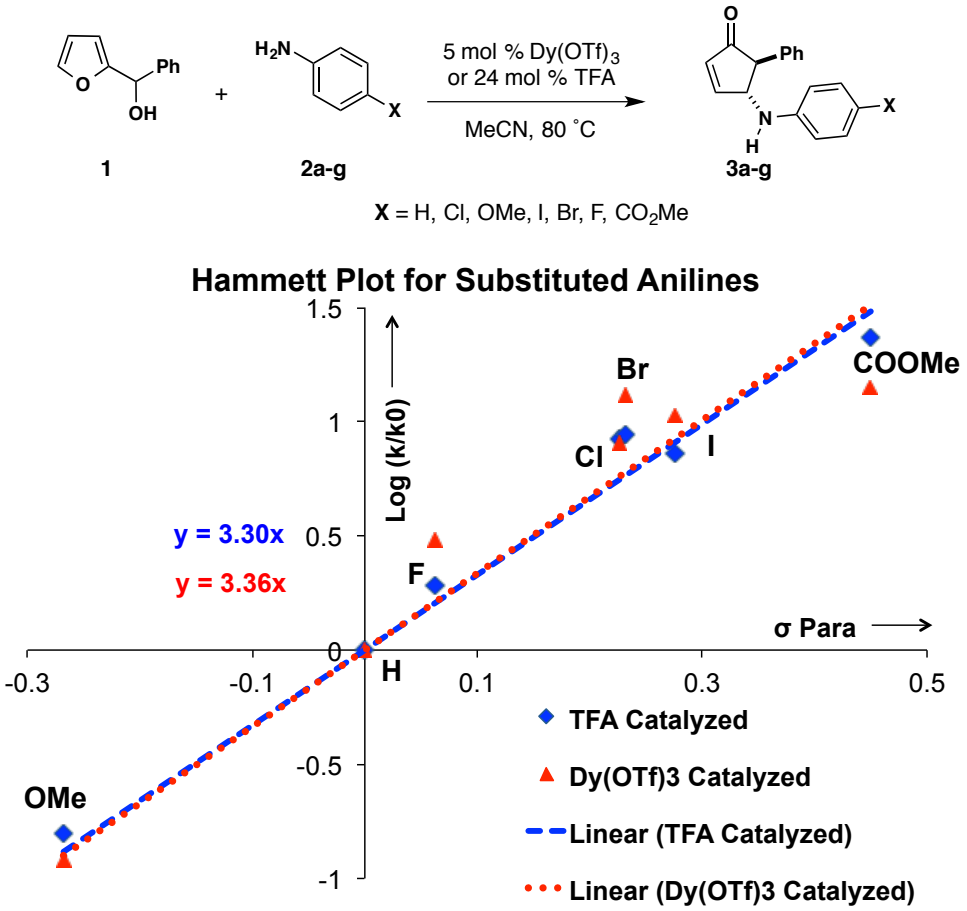
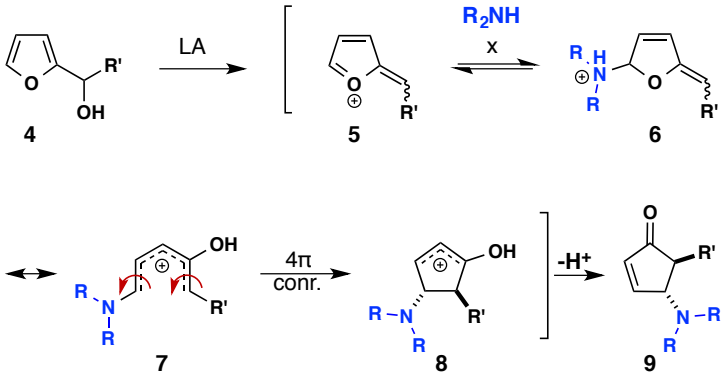


Figure 5.3. Effect of *para*-substituents of aniline on the reaction rate under Lewis and Brønsted acid catalysis.

Examining the proposed mechanism (Scheme 5.1) of the reaction in light of the mechanistic data leads to two possible explanations for the observed trends with both dysprosium and TFA. The first explanation is that ring opening of aminal **6** is the rate limiting step of the reaction. This aminal has never been observed in the aza-Piancatelli rearrangement, but Denisov,[75] Wu[43,159] and Read de Alaniz[139] have described the analogous acetal species (**11**) as isolable and stable (Figure 5.4).



Scheme 5.1. Proposed mechanism of the aza-Piancatelli rearrangement.

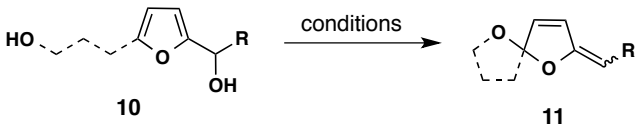
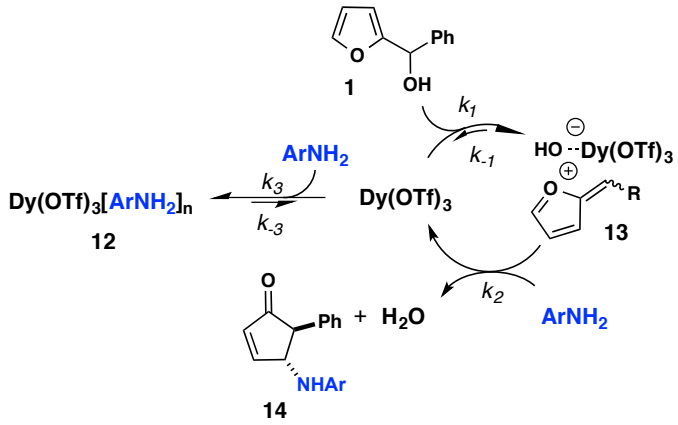


Figure 5.4. Formation of observable and isolable acetal structures.

If ring opening of the aminal is the rate determining step in the reaction, a negative ρ value corresponding to stabilization of the positive charge generated would be expected. Since this is not the case, an alternative explanation is that preferential binding of $Dy(OTf)_3$ by the aniline occurs. This binding event may account for both the observed zero order reaction profile as well as the positive ρ value. The proposed model for this off-cycle binding to dysprosium is pictorially represented in Scheme 5.2, and a rate equation based on a Michaelis-Menten kinetics model with competitive inhibition was also derived.[160] The steady state equation can be expressed in terms of the dysprosium catalyst, furylcarbinol (**1**) and aniline (**2**) (Equation 5.1). In this model, the aniline serves the role of both nucleophile and inhibitor, and we assume that the aniline and dysprosium bind strongly (**12**) ($k_3 >> k_1$ and k_{-3}) and that the capture of the oxocarbenium (**13**) is fast ($k_2 >> k_1$ and k_{-1}).



Scheme 5.2. Proposed off-cycle binding in the catalytic cycle of the aza-Piancatelli rearrangement.

Equation 5.1. Steady-state rate expression for the aza-Piancatelli rearrangement.

$$\frac{d[\mathbf{3}]}{dt} = \frac{k_1 k_{-3}}{k_3} \frac{[\mathbf{1}][\mathbf{Dy(OTf)_3}]}{[\mathbf{2}]}$$

The rate expression clearly shows the rate dependence on both the ratio of furylcarbinol **1** to aniline **2** ([**1**]/[**2**]). It also shows the effect of strong binding between the aniline and dysprosium (k_{-3}/k_3), where the equilibrium lies further toward the formation of complex **12** in reactions with electron rich anilines than electron poor anilines. Although we did not isolate a dysprosium-aniline complex, such aniline-dysprosium complexes have been reported in the literature.[161,162] We did note the formation of a precipitate during reactions with morpholine, which likely corresponds to a morpholine-dysprosium complex (Chapter 4, Scheme 4.1). Additional experiments to study the formation of this off-cycle complex (**12**) were performed by varying the ratio of furylcarbinol to aniline (Figure 5.5). When an excess of furylcarbinol was used, the initial rate was 1.1 mM/min, while the reaction with excess aniline was slower at 0.26 mM/min. Subsequent addition of aniline or furylcarbinol to create equimolar reaction mixtures resulted in reaction rates of 6.5 mM/min and 5.1 mM/min, respectively. Although these results indicate that reaction rates may be positively

influenced if there is an excess of furylcarbinol, in practice this is not the case due to decomposition of **1**, as well as increased formation of Friedel–Crafts alkylation products.

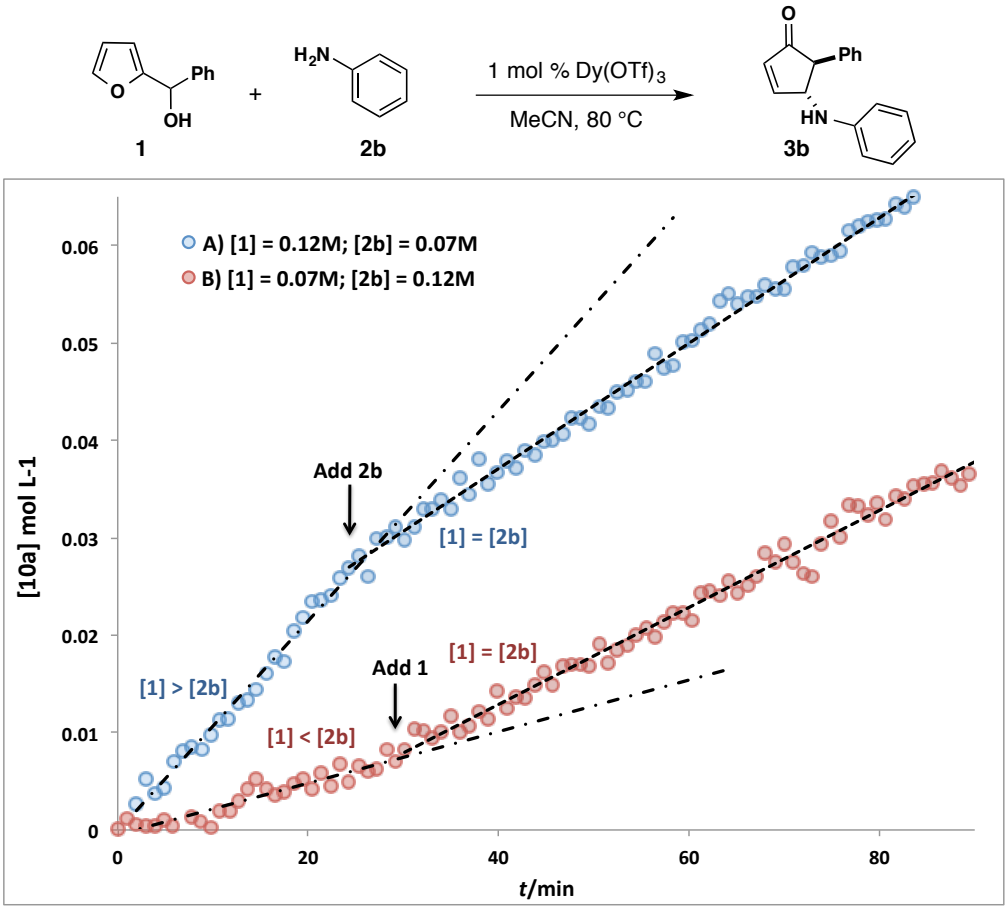


Figure 5.5. Effect of excess aniline or furylcarbinol on the aza-Piancatelli rearrangement.

Finally, we performed a competition experiment with an electron rich and an electron poor aniline. The reactions were set up using phenyl furylcarbinol (**1**) (0.125M) and equimolar amounts of *p*-chloroaniline (**2c**) (0.0625M) and *p*-methoxyaniline (**2d**) (0.0625M) with either 5 mol % $Dy(OTf)_3$ or 24 mol % TFA catalyst. To our surprise, we found that the electron rich *p*-methoxyaniline, which forms a stronger complex with dysprosium, outcompetes *p*-chloroaniline in the reaction with either catalyst (Figure 5.6).

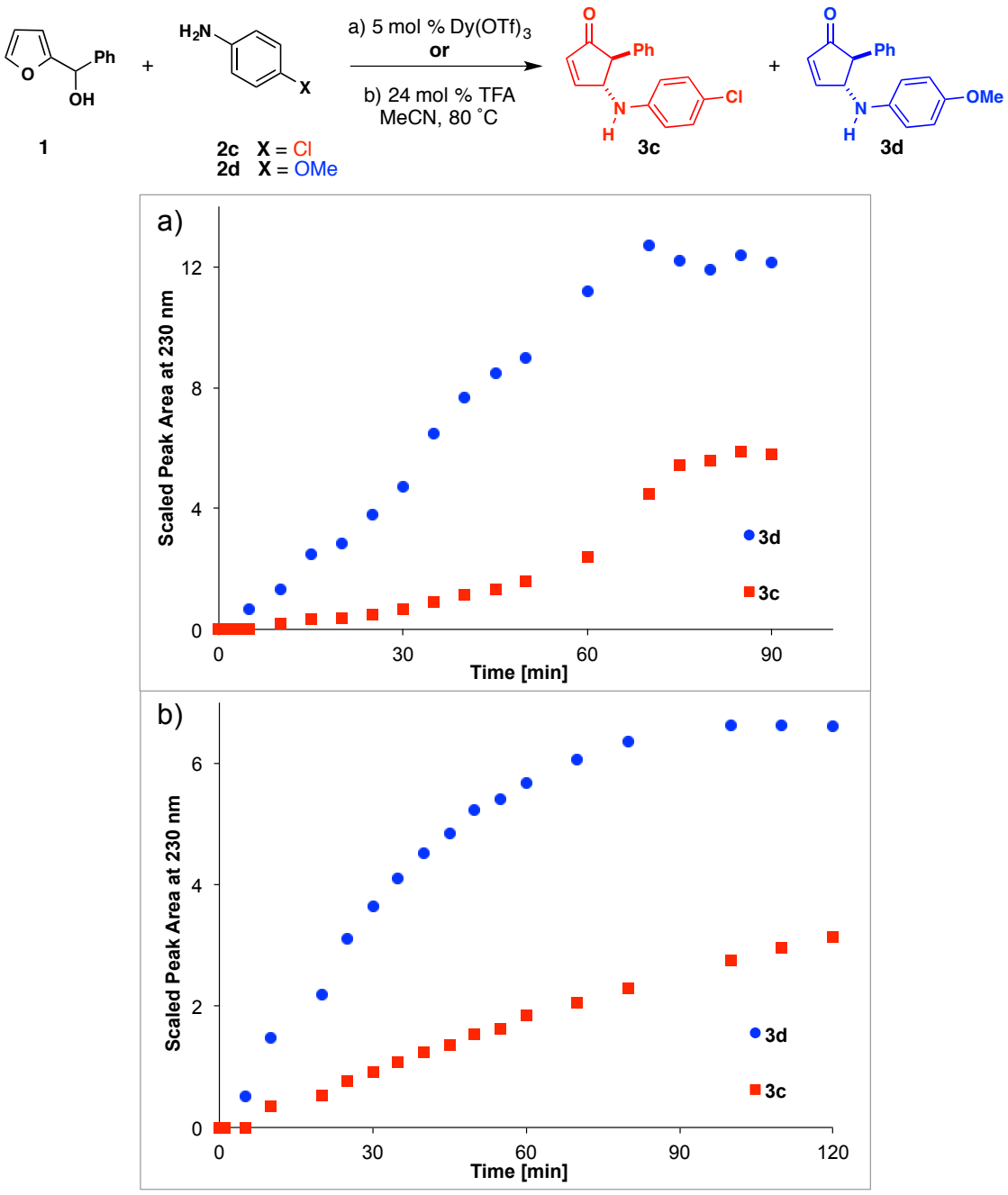
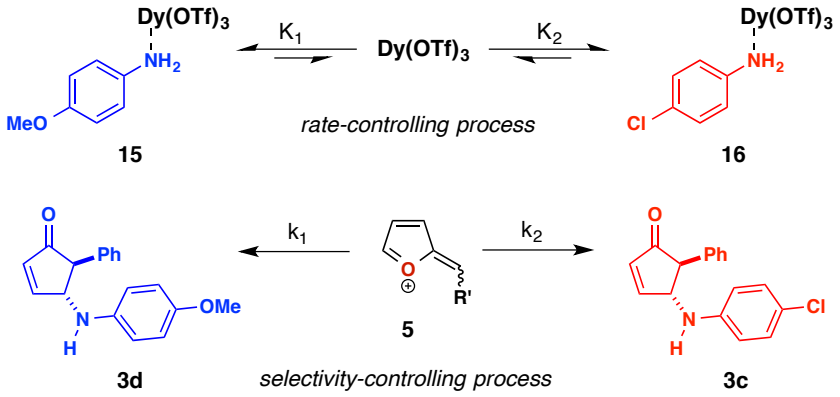


Figure 5.6. Competition between anilines. (a) Dy(OTf)3 catalyzed reaction; (b) TFA catalyzed reaction.

Examining our proposed reaction mechanism, we determined that the initial rate of the reaction is controlled by the formation of dysprosium-*p*-methoxyaniline complex **15**. However, upon formation of the oxocarbenium **5**, electron-rich *p*-methoxyaniline

outcompetes electron-poor *p*-chloroaniline. Once *p*-methoxyaniline is expended, an increase in the rate of formation of the **3c** is observed (approximately 90 min), corresponding to a shift of the equilibrium of the dysprosium complex toward the formation of **16**. The reaction with TFA proceeds analogously with electron-rich *p*-methoxyaniline modulating the concentration of TFA available to catalyze formation of the oxocarbenium **5**. In summary, these results indicate that the selectivity determining step and the rate-controlling processes are decoupled in the aza-Piancatelli rearrangement (Scheme 5.3).



Scheme 5.3. Rate and selectivity determining processes in the aza-Piancatelli rearrangement.

In conclusion, our mechanistic studies allowed us to gain a greater understanding of the intricacies of the aza-Piancatelli rearrangement. We were able to answer some of the questions posed at the beginning of the investigation. First, we determined that the reaction with $Dy(OTf)_3$ does not rely on adventitious generation of triflic acid. We also experimentally confirmed our empirically observed effects of electronics on the rate of the reaction. Finally, we found that the formation of a dysprosium-aniline complex is responsible for the observed reaction rates, but that this rate-controlling step is decoupled from the chemoselectivity of the reaction.

In the future, we hope to continue to use this information to guide the development of new reactions with furylcarbinols as well as dysprosium-catalyzed reactions. Ideally, we would find reaction conditions where an additional ligand could control the formation of the amine-dysprosium complex to allow for the use of more basic alkylamines in the rearrangement.

5.4. Experimental Procedures

Materials and Methods. Furan-2-yl(phenyl)methanol was prepared according to literature precedent of a similar transformation by reacting furfural with phenylmagnesium bromide.[1] Dysprosium(III) trifluoromethanesulfonate ($Dy(OTf)_3$) was used as received from Strem Chemicals, Inc.. All other materials were obtained from conventional suppliers and used as received. Flash chromatography was carried out using Sorbtech silica gel 60A (230x400 mesh). Thin-layer chromatography (TLC) was performed on Sorbtech precoated silica gel plates and was visualized by irradiation with UV light or staining with potassium permanganate solution.

Kinetic studies monitored by in-situ FTIR were conducted with a Mettler-Toledo ReactIR iC 10 fitted with a Diamond ATR probe. Reaction temperatures were controlled using a Heidolph temperature modulator. 2-Methoxynaphthalene was used as an internal standard in some experiments as specified, and had no effect on the reaction, as confirmed by monitoring reactions via ReactIR and HPLC-MS both with and in the absence of the standard.

^{1}H NMR spectra were recorded on Varian Spectrometers (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 MHz). Data for ^{13}C NMR

spectra are reported as follows: shift (δ ppm), multiplicity and coupling constant (Hz). IR spectra were recorded on a Jasco FT/IR 4100 or PerkinElmer Spectrum 100 FT-IR and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facilities.

NMR experiment set-up.

NMR experiments were performed on a 600 MHz Varian Spectrometer. The samples were prepared in MeCN-d3 with dimethyl terephthalate as an internal standard (1.45 mg, 0.0075 mmol). An initial spectrum of phenyl furylcarbinol (**1**) (2.6 mg, 0.015 mmol) and *p*-iodoaniline (3.3 mg, 0.015 mmol) in 900 μL MeCN-d3 was obtained. The sample was removed from the magnet, treated with a solution of $Sc(OTf)_3$ in MeCN-d3 (100 μL = 0.37 mg, 0.00075 mmol) and replaced in the magnet after quickly shaking the sample for data collection.

To set up the NMR experiment for continual data collection:

Join Experiment 2 (jexp2, return)

Set gain.

nt=16

pad=1

array [return]

parameter to be arrayed? pad

number of steps? xx (each step is one transient, nt=16 takes 1 min 57 sec =117 sec)

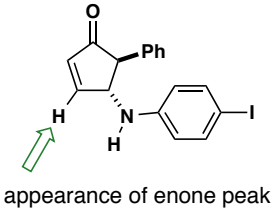
starting value? 1

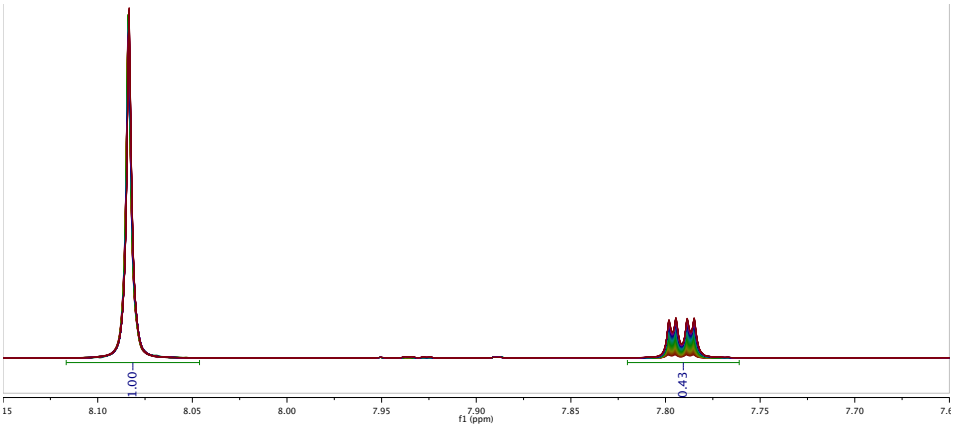
array increment? 0

da (display array)

time (displays how long experiment will take. This number is determined by the number of steps in the experiment)

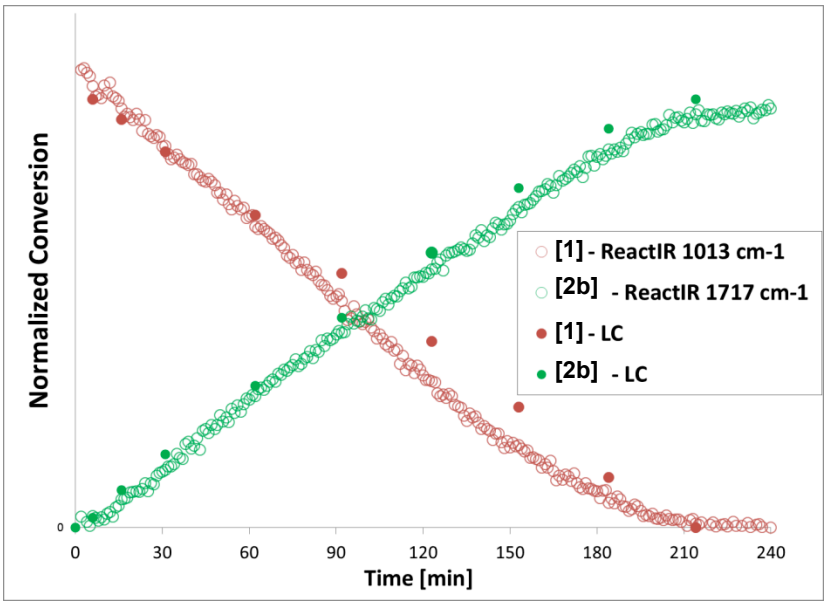
For the above reaction, nt=16, number of steps = 72 to monitor the reaction over the course of 6h.





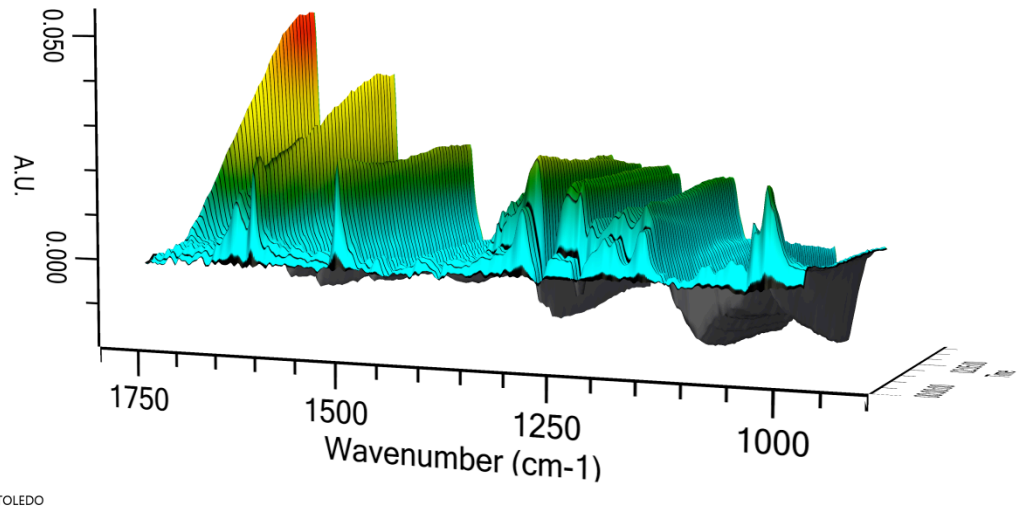
Validation of FTIR for Reaction Analysis. Validation of FTIR as a suitable technique for in-situ reaction analysis was performed through reaction sampling and HPLC-MS analysis of reaction conversion and product formation as a function of time. The reaction was sampled by withdrawal of approximately 5 microliter aliquots of the reaction solution and diluted with methanol at room temperature. Samples were analyzed by HPLC-MS immediately. HPLC-MS analysis was conducted with an Agilent Eclipse XDB C18, 3.5 µm, 3.0 x 75 mm column. HPLC-MS analysis was conducted with an Agilent Eclipse XDB C18, 3.5 µm, 3.0 x 75 mm column (standard column conditions – A = water (0.05% TFA), B = acetonitrile (0.05% TFA), 0.400 mL/min, initial, 38% B – linear gradient to 100% B over 20 min).

Tandem Reaction Monitoring by ReactIR and HPLC-MS

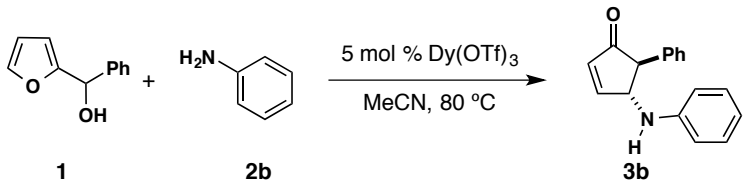


Analysis of the reaction conversion time course by FTIR and sampling methods were in agreement.

Sample FTIR Spectra of $Dy(OTf)_3$ - Catalyzed Zero-Order Reaction



General Procedure for Kinetic Experiments

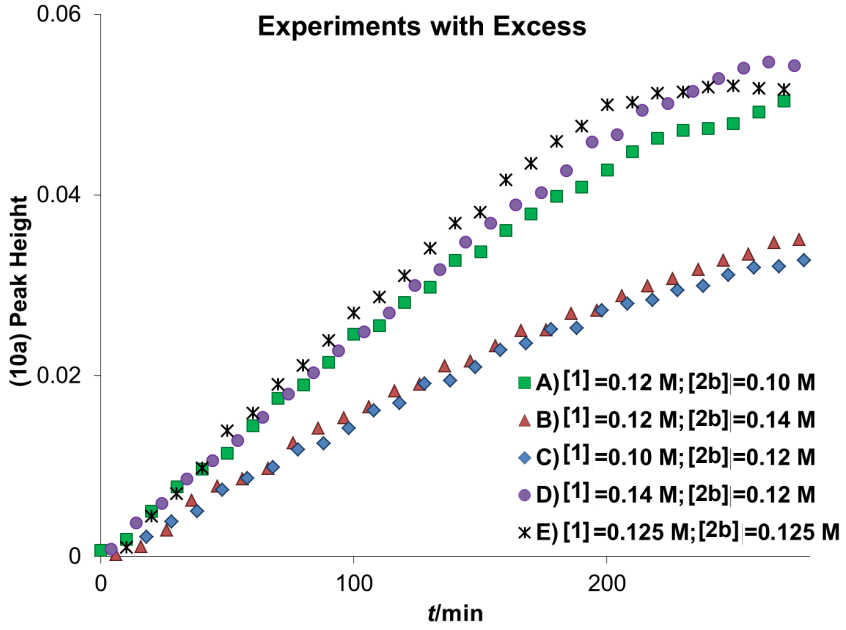


To a 10 mL vial with PTFE-silicon septum and open screw-cap was added 2 mL of acetonitrile. The vial was placed in a pre-heated oil-bath at 80 °C and allowed to equilibrate. After taking a background scan in hot solvent, furan-2-yl(phenyl)methanol **1** (44.0 mg, 0.250 mmol, 0.125 M) and aniline **2b** (23.0 mg, 0.250 mmol, 0.125 M) were added to the pre-equilibrated acetonitrile. After a stable FTIR signal was observed, $Dy(OTf)_3$ (7.6 mg, 0.013 mmol, 5 mol %) catalyst was added. Reaction progress was monitored by FTIR using two peaks: 1013 cm^{-1} for the consumption of furylcarbinol **1**, and 1715 cm^{-1} for the appearance of cyclopentenone **3b**.

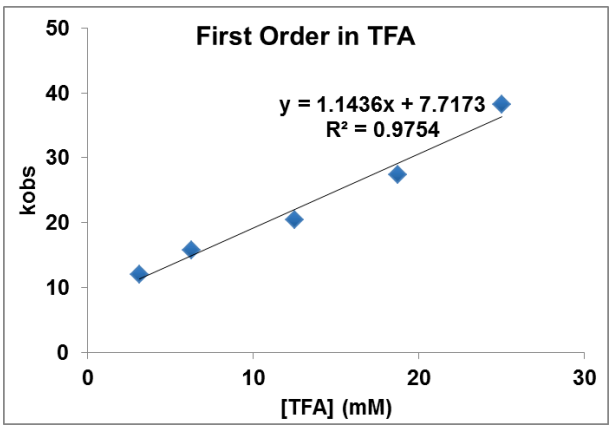
Experiments with Same Excess. As an internal standard, 20 μL of a 0.58 M stock solution of 2-methoxynaphthalene was used in each reaction. On the ReactIR, a background scan was taken in 65 °C acetonitrile and 2-methoxynaphthalene. Stock solutions of furylcarbinol **1** and aniline **2b** were injected, followed by subsequent addition of solid $Dy(OTf)_3$. All experiments in same excess used the same concentration of $Dy(OTf)_3$ (0.00625 M) and a total reaction volume of 2 mL. The following table summarizes the molarities and excesses of furylcarbinol **1** to aniline **2b**.

Experiment	$[1]_0$ / M	$[2b]_0$ / M	[2b]-[1] / M
Same excess [**1**]	0.12	0.10	- 0.02
Same excess [**1**]	0.14	0.12	- 0.02
Same excess [**2b**]	0.10	0.12	0.02
Same excess [**2b**]	0.12	0.14	0.02

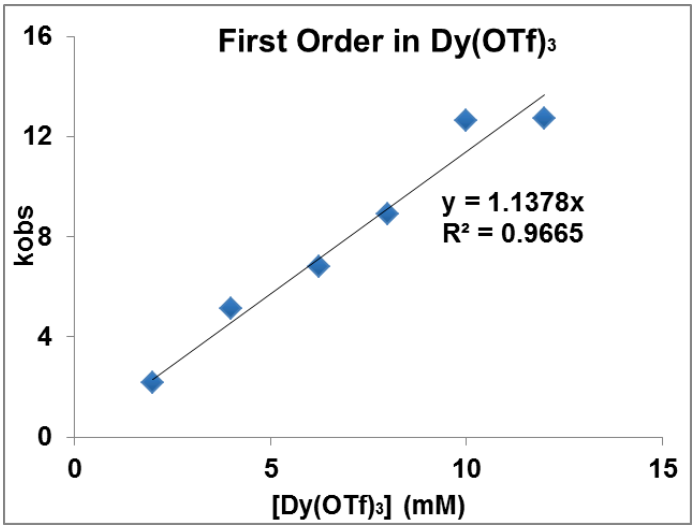
The subsequent reaction solutions were analyzed by HPLC to check conversion of furylcarbinol **1** to the cyclopentenone **3b**. The formation of cyclopentenone **3b**, as monitored by ReactIR, is graphed without normalization below.



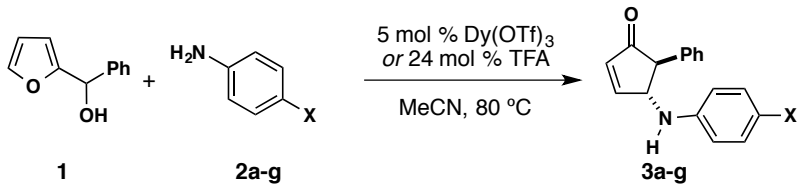
Order in Trifluoroacetic Acid Catalyst. Stock solutions of **1**, **2b**, and trifluoroacetic acid (TFA) in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **1** and **2b** and were run at 65 °C. Concentrations of TFA were as follows: 3.125, 6.25, 12.5, 18.75, 25, and 30 mM. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **1** and aniline **2b** were added. When a steady signal was reached on the FTIR, an appropriate portion of the TFA stock solution was injected. The slope of the initial rate of formation of **2b** in each reaction was used in finding the order in TFA. The positive and linear fit implies that the Piancatelli reaction is first order in TFA. *Note*: these are not absolute rate (k) constants, but relative k values.



Order in $Dy(OTf)_3$ Catalyst. Stock solutions of **1** and **2b** in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **1** and **2b** and were run at 65 °C. Concentrations of $Dy(OTf)_3$ were as follows: 2, 4, 6.25, 8, 10, and 12 mM. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **1** and aniline **2b** were added. When a steady signal was reached on the FTIR, the appropriate amount of $Dy(OTf)_3$ was added as a solid. The slope of the initial rate of formation of **2b** in each reaction was used in finding the order in $Dy(OTf)_3$. The positive and linear fit implies that the Piancatelli reaction is first order in $Dy(OTf)_3$. *Note*: these are not absolute rate (k) constants, but relative k values.



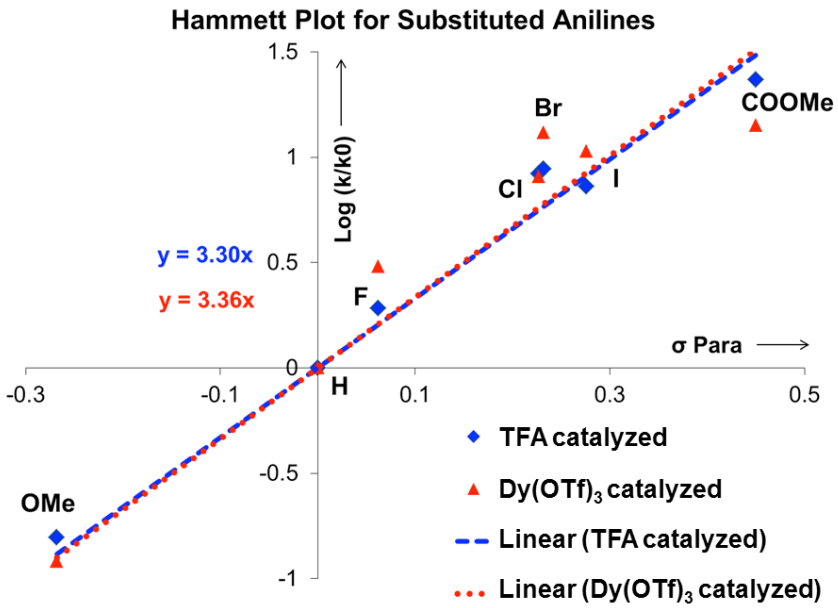
Linear Free Energy Relationships



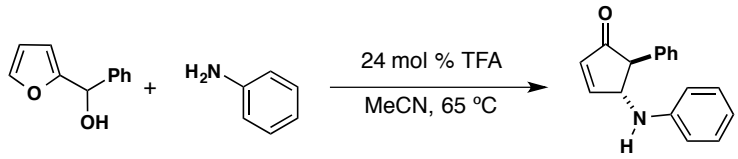
1 **2a-g** **3a-g**

X = H, Cl, OMe, I, Br, F, CO_2Me

A stock solution of **1** in acetonitrile was prepared and used within two days. Reactions were 0.125 M in **1** and the substituted aniline **2a-g** and were run at 80 °C on a 2 mL scale. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **1** and the substituted aniline **2a-g** were added. When a steady signal was reached on the FTIR, $Dy(OTf)_3$ (7.6 mg, 0.013 mmol, 5 mol % relative to furylcarbinol) was added as a solid. For the TFA-catalyzed experiments, 0.02 mL of a 0.3 M TFA stock solution was used to provide a 2 mL reaction solution that was 30 mM in TFA (24 mol % relative to furylcarbinol **1**). The slopes of initial rate of formation of **3a-g** in individual reactions were used in graphing the Hammett Plots. *Note*: these are not absolute rate (k) constants, but relative k values.

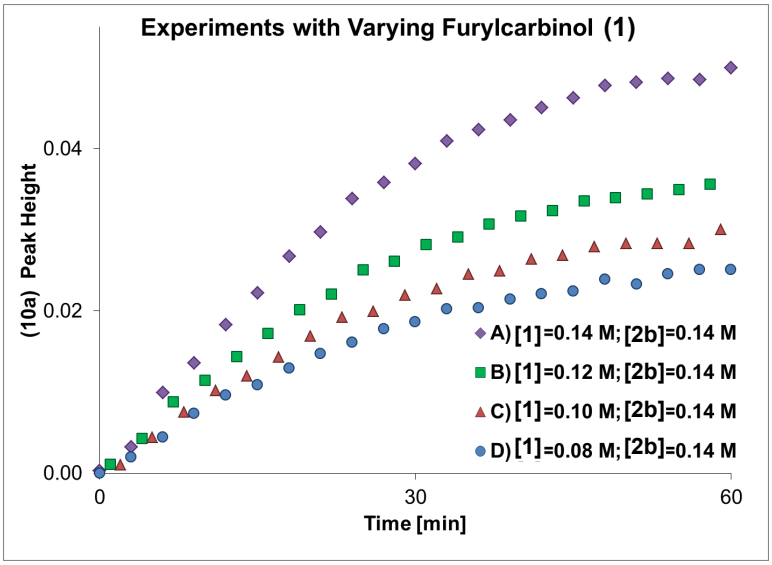


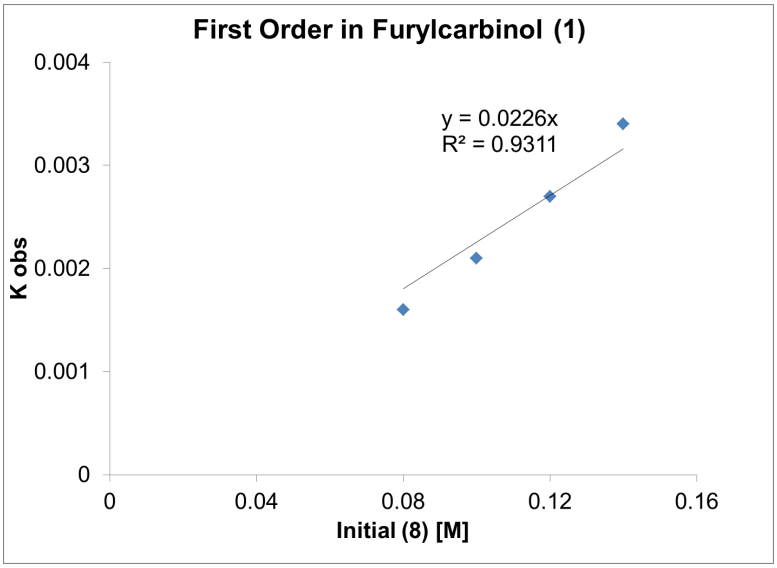
Order in Furylcarbinol 1, TFA Catalyzed



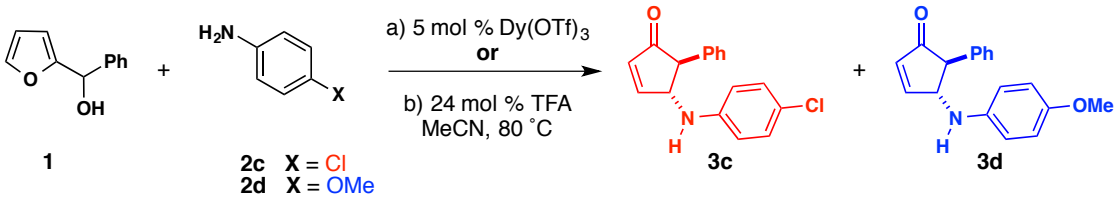
1 **2b** **3b**

Stock solutions of **1** and **2b** in acetonitrile were prepared and used within two days. Reactions were 0.125 M in **1** and **2b** and were run at 65 °C on a 2 mL scale. To a pre-heated vial of acetonitrile, the stock solutions of furylcarbinol **1** and aniline **2b** were added. When a steady signal was reached on the FTIR, 0.02 mL of a 0.3 M TFA stock solution was used to provide a 2 mL reaction solution that was 30 mM in TFA (24 mol % relative to aniline **2b**). The slope of the initial rate of formation of **3b** in each reaction was used in finding order in furylcarbinol. *Note*: these are not absolute rate (k) constants, but relative k values.





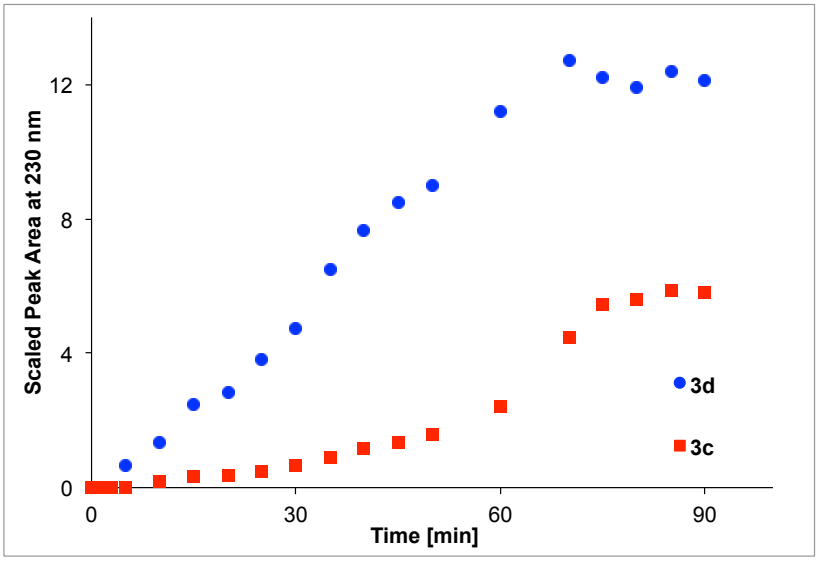
Competition Experiments



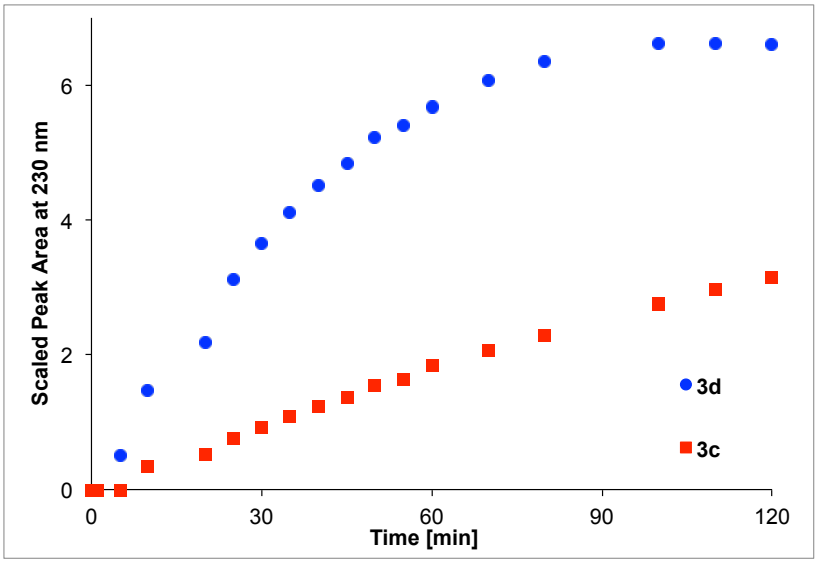
Competition experiments were conducted at 80 °C with 4-chloroaniline **2c** and 4-methoxyaniline **2d** to make cyclopentenones **3c** and **3d**, respectively. As a standard, 0.1 mL of a 0.101 M stock solution of 2-methoxynaphthalene for every 1 mL reaction solution was used. A 3 mL solution of acetonitrile and 2-methoxynaphthalene was preheated to 80 °C. Furylcarbinol **1** was added by dissolution from a tared syringe, followed by solid aniline **2c** or **2d**. A sample was taken at this point for analysis of initial conditions. Either $Dy(OTf)_3$ (5 mol % relative to furylcarbinol **1**) or TFA (24 mol % relative to furylcarbinol **1**) was added. The reactions were sampled by taking approximately 5 µL aliquots and dilution with approximately 1 mL of methanol and immediately analyzed by HPLC-MS.

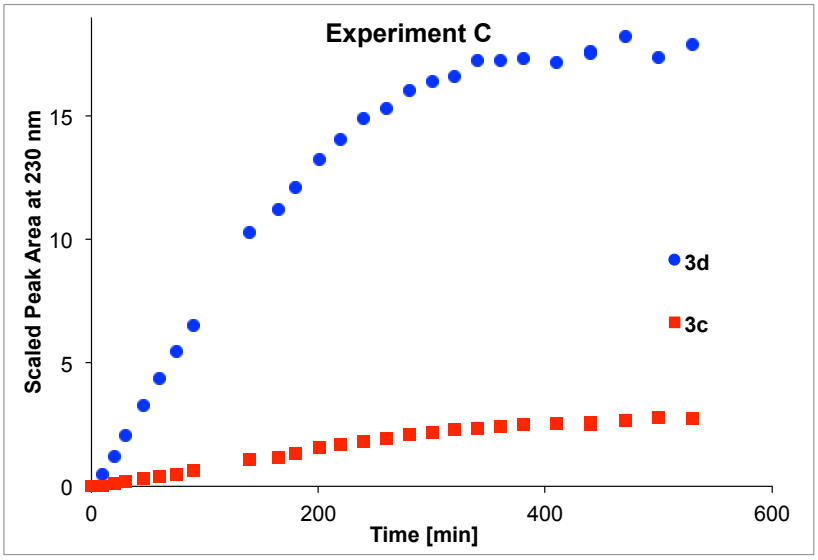
Experiment	Catalyst	$[1]_0$ / M	$[2c]_0$ / M	$[2d]_0$ / M	Catalyst / M
A	$Dy(OTf)_3$	0.125	0.0625	0.0625	0.0063
B	TFA	0.125	0.0625	0.0625	0.030
C	$Dy(OTf)_3$	0.125	0.125	0.125	0.0063

Experiment A

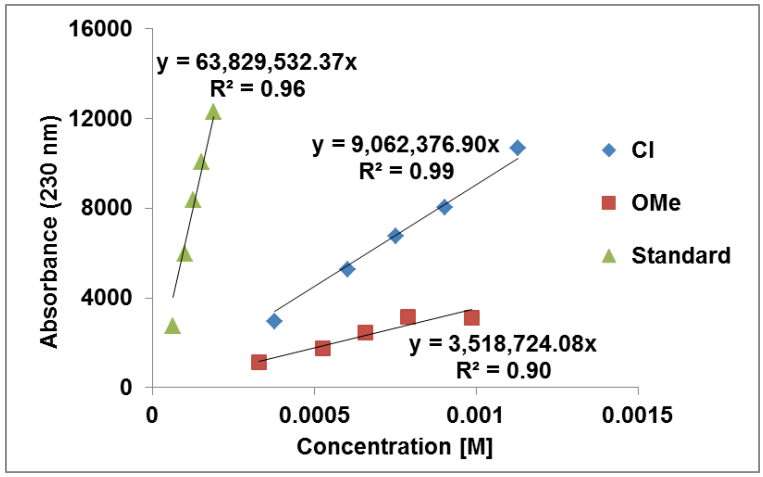


Experiment B





A calibration curve was created between the two cyclopentenone products **3c** and **3d** and the standard, 2-methoxynaphthalene, to determine the selectivity for either product over time. Each cyclopentenone was synthesized by the standard procedure[2] and purified by flash column chromatography (1:6 to 1:4 EtOAc:hexanes). Relative UV absorptivities at 230 nm with 8 μL injections were analyzed by HPLC-MS for the following calibration curves:



The column conditions were as follows:

A= Water, 0.05% TFA

B= Acetonitrile, 0.05% TFA

Start 10%B

6.5 min 45%B

18 min 65%B

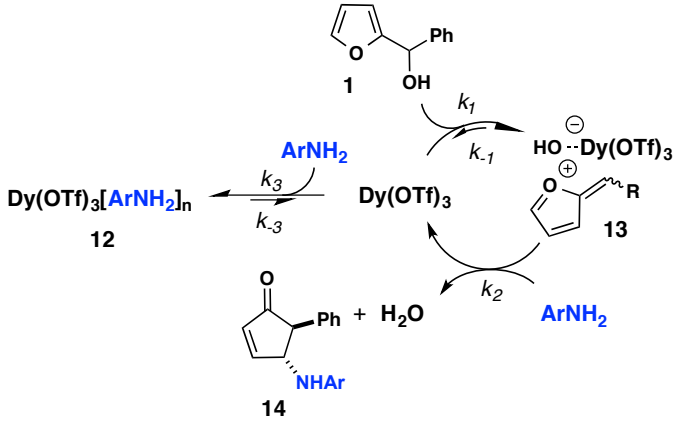
20 min 100%B

Flow rate 0.400 mL/min

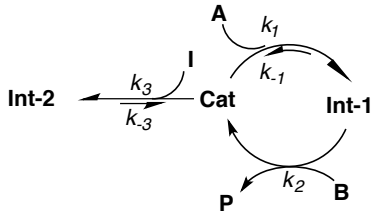
Agilent Eclipse XDB C18, 3.5 µm, 3.0 x 75 mm column

Derivation of Steady State Rate Law

The proposed mechanism based on the competitive inhibition model follows the scheme:



Or drawn in general:



Assumptions:

Mass balance for the catalyst is given by

1) $[cat_{tot}] = [cat_0] = [cat] + [Int1] + [Int2]$

By using steady state approximations,

2a) $$\frac{d\,[cat]}{dt} \approx 0 \approx -k_1\,[cat][A] + k_{-1}\,[Int1] + k_2\,[B][Int1] - k_3[I][cat] + k_{-3}[Int2]$$

2b) $$\frac{d\,[Int1]}{dt} \approx 0 \approx k_1\,[cat][A] - k_{-1}[Int1] - k_2[Int1][B]$$

2c) $$\frac{d\,[Int2]}{dt} \approx 0 \approx k_3[cat][I] - k_{-3}[Int2]$$

Rate of product formation:

$$\frac{d\,[P]}{dt} = k_2[Int1][B]$$

Define [cat] in terms of [Int1] by using 2b):

$$k_1[cat][A] = k_{-1}[Int1] + k_2[Int1][B]$$

$$[cat] = \frac{k_{-1}[Int1] + k_2[Int1][B]}{k_1[A]} = \frac{(k_{-1} + k_2\,[B])[Int1]}{k_1[A]}$$

Substitute [cat] into 2c)

$$0 = k_3\,[I]\left(\frac{(k_{-1} + k_2\,[B])[Int1]}{k_1[A]}\right) - k_{-3}\,[Int2]$$

$$[Int2] = \frac{k_3\,(k_{-1} + k_2\,[B])[Int1][I]}{k_{-3}\,k_1[A]}$$

Substitute [Int2] into $[cat_{tot}]$:

$$[cat_{tot}] = \frac{(k_{-1} + k_2\,[B])[Int1]}{k_1[A]} + [Int1] + \frac{k_3[Int1][I]\,(k_{-1} + k_2\,[B])}{k_{-3}\,k_1[A]}$$

$$[cat_{tot}] = [Int1]\left(\frac{(k_{-1} + k_2[B])}{k_1[A]}\right) + [Int1] + [Int1]\left(\frac{k_3[I](k_{-1} + k_2[B])}{k_{-3}\,k_1[A]}\right)$$

$$[cat_{tot}] = [Int1]\frac{k_{-3}(k_{-1} + k_2[B]) + k_{-3}\,k_1[A] + k_3\,[I](k_{-1} + k_2[B])}{k_{-3}\,k_1[A]}$$

$$[Int1] = \frac{[cat_{tot}]\,k_{-3}\,k_1[A]}{k_{-3}(k_{-1} + k_2[B]) + k_{-3}\,k_1[A] + k_3\,[I](k_{-1} + k_2[B])}$$

Therefore, rate of product formation is:

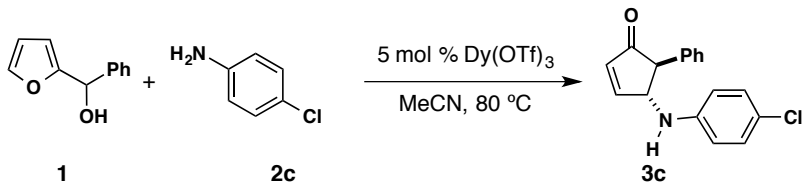
$$\frac{d\,[B]}{dt} = k_2\,[B][Int1] = \frac{k_1\,k_2\,k_{-3}\,[A]\,[B]\,[cat_{tot}]}{k_{-3}(k_{-1} + k_2[B]) + k_{-3}\,k_1[A] + k_3\,[I](k_{-1} + k_2[B])}$$

If I = B,

$$\frac{d\,[P]}{dt} = \frac{k_1\,k_2\,k_{-3}\,[A]\,[B]\,[cat_{tot}]}{k_{-3}(k_{-1} + k_2[B] + k_1[A]) + k_3\,(k_{-1}[B] + k_2[B]^2)}$$

If we assume the terms k_3 and k_2 are the most important (largest magnitude) this reduces to:

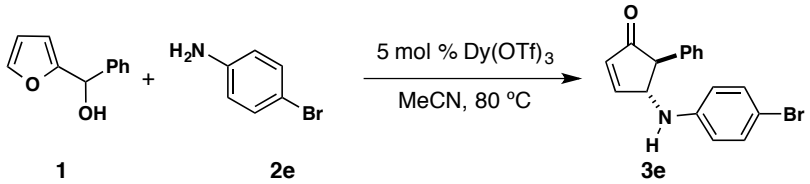
$$\frac{d\,[P]}{dt} = \frac{k_1\,k_{-3}\,[A]\,[cat_{tot}]}{k_3[B]}$$



1 2c 3c

4-((4-Chlorophenyl)amino)-5-phenylcyclopent-2-en-1-one (3c): According to the general procedure $Dy(OTf)_3$ (4.4 mg, 0.0072 mmol, 0.05 equiv) was added to furan-2-

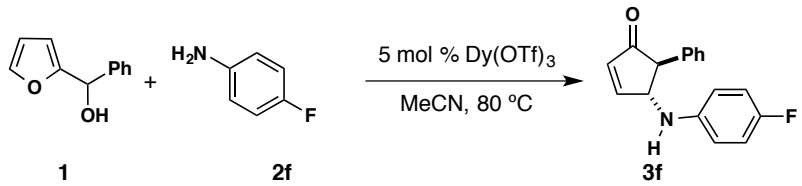
yl(phenyl)methanol **1** (25.0 mg, 0.144 mmol, 1 equiv) and 4-chloroaniline **2c** (18.3 mg, 0.144 mmol, 1 equiv) in 3 mL of acetonitrile. The resulting reaction mixture was heated to 80 ºC for 10 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **3c** (41.2 mg, 90%) as a solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 5.8, 2.3 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.32 – 7.28 (m, 1H), 7.14 – 7.10 (m, 2H), 7.08 – 7.04 (m, 2H), 6.44 – 6.40 (m, 3H), 4.70 (q, *J* = 2.2 Hz, 1H), 4.13 – 4.02 (m, 1H), 3.36 (d, *J* = 2.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.4, 161.4, 144.8, 138.0, 135.1, 129.4, 129.2, 128.0, 127.6, 123.4, 115.0, 63.5, 60.2 ppm; **IR** (thin film) 3375, 3060, 3029, 2924, 2854, 1870, 1803, 1702, 1597, 1492, 1314, 1248, 1178, 1090 cm^{-1}; **HRMS** (ESI) m/z 306.0655 (306.0662 calcd for $C_{17}H_{14}ClNNaO^+$ $[M + Na]^+$); **MS** (ESI) m/z 284.09 (100%), 286.1 (34), 285.10 (20), 287.10 (6) (284.08, 286.08, 285.09, 287.08 calcd for $C_{17}H_{15}ClNO^+$ $[M + H]^+$).



1 **2e** **3e**

4-((4-Bromophenyl)amino)-5-phenylcyclopent-2-en-1-one (3e): According to the general procedure $Dy(OTf)_3$ (4.4 mg, 0.0072 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **1** (25.0 mg, 0.144 mmol, 1 equiv) and 4-bromoaniline **2e** (24.7 mg, 0.144 mmol, 1 equiv) in 3 mL of acetonitrile. The resulting reaction mixture was heated to 80 ºC for 15 minutes. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 5 mL). The combined organic

layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **3e** (36.4 mg, 76%) as a solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 5.8, 2.4 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.33 – 7.27 (m, 1H), 7.23 – 7.17 (m, 2H), 7.16 – 7.10 (m, 2H), 6.44 (dd, *J* = 5.8, 1.7 Hz, 1H), 6.40 – 6.36 (m, 2H), 4.73 – 4.70 (m, 1H), 4.00 (d, *J* = 8.5 Hz, 1H), 3.36 (d, *J* = 2.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.3, 161.2, 145.2, 138.0, 135.2, 132.3, 129.2, 128.0, 127.7, 115.5, 110.6, 63.5, 60.2 ppm; **IR** (thin film) 3369, 3061, 3027, 2920, 1700, 1591, 1487, 1313 cm^{-1}; **HRMS** (ESI) m/z 350.0145 (350.0156 calcd for $C_{17}H_{14}BrNNaO^+$ $[M + Na]^+$); **MS** (ESI) m/z 352.02 (100%), 350.02 (96), 351.02 (18), 353.02 (15) (352.01, 350.02, 351.02, 353.02 calcd for $C_{17}H_{14}BrNNaO^+$ $[M + Na]^+$).



1 **2f** **3f**

4-((4-Fluorophenyl)amino)-5-phenylcyclopent-2-en-1-one (3f): According to the general procedure $Dy(OTf)_3$ (8.7 mg, 0.014 mmol, 0.05 equiv) was added to furan-2-yl(phenyl)methanol **1** (50.0 mg, 0.287 mmol, 1 equiv) and 4-fluoroaniline **2f** (27.0 μL, 0.287 mmol, 1 equiv) in 3 mL of acetonitrile. The resulting reaction mixture was heated to 80 ºC for 2.5 hours. The reaction was then quenched with 5 mL of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **3f** (70.5 mg, 92%) as a solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.15 – 7.08 (m, 2H), 6.88 – 6.80 (m, 2H), 6.48 – 6.44 (m, 2H), 6.42 (dd, *J* = 5.8, 1.7 Hz, 1H), 4.69 (s, 1H),

3.87 (s, 1H), 3.37 (d, J = 2.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.5, 161.7, 156.6 (d, J = 237.0 Hz), 142.5, 138.1, 135.0, 129.2, 128.0, 127.57, 116.0 (d, J = 22.5 Hz), 115.2 (d, J = 7.5 Hz), 64.2, 60.2; **IR** (thin film) 3370, 3061, 3029, 2918, 1701, 1505, 1309, 1213, 1156 cm^{-1}; **HRMS** (EI^+) m/z 267.1053 (267.1059 calcd for $C_{17}H_{14}FNO^+$ $[M]^{\bullet+}$).

6. Development of an Asymmetric Aza-Piancatelli Rearrangement

6.1. The Importance of an Asymmetric Transformation

For today's chemists, the ability to access a single enantiomer of a molecule is of paramount importance, and the field of new reaction development is dominated by novel asymmetric reactions. Following the development of the aza-Piancatelli rearrangement, we sought to further the understanding and utility of this reaction and became interested in exploring an asymmetric aza-Piancatelli rearrangement. Developing an asymmetric aza-Piancatelli is a significant, but important, challenge since no asymmetric variant of the Piancatelli rearrangement has been reported despite the reaction being known for over thirty years.[39]

In 1848, Louis Pasteur discovered that synthetic tartaric acid, when crystallized, is composed of two different separable crystals, each of which rotates light in opposite directions.[163] This discovery of chirality in organic molecules laid the foundation for much of the chemistry we know today. Selective synthesis of single enantiomers forms the basis of much of the new chemistry that is developed, and is constantly applied in total synthesis. More importantly, all of life relies on and is based on chiral molecules, including amino acids, DNA, RNA, proteins, and enzymes. Because of the inherent chirality of biological molecules, it is often the case that one enantiomer of a target molecule will bind preferentially over another. Perhaps the most poignant example of the importance of chirality for synthetic chemists is the thalidomide case. Prescribed to scores of pregnant women as an antiemetic in the 1950s and 60s, it was soon discovered that thalidomide, specifically the (S)-enantiomer (**2**), is a teratogen (Figure 6.1).[164] Thousands of children were born with malformed limbs, and many thousands more were never born. It was later

learned that the (S)-enantiomer is responsible for the devastating effects. While the (R)-enantiomer (**1**) is not itself teratogenic, thalidomide racemizes under physiological conditions, making administration of a single enantiomer useless. This tragic and unfortunate example truly highlights the importance of asymmetric synthesis, as well as the importance of clinical trials and thorough investigations of drug metabolisms.

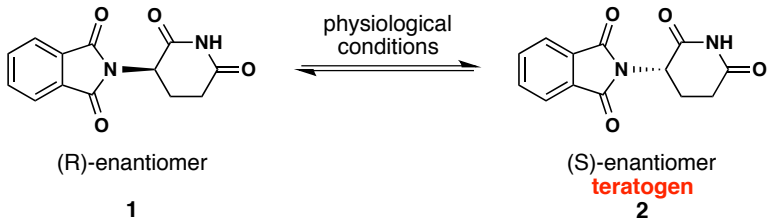


Figure 6.1. (R)- and (S)-enantiomers of thalidomide.

An asymmetric aza-Piancatelli rearrangement is desirable for its application to the total synthesis of natural products, such as homoharringtonine (**3**) and stemonamine (**4**). It would also be valuable for the enantioselective synthesis of an hNK1 inhibitor since enantiomer **5** displays an IC_{50} of 2.3 nM while the racemic sample (**6**) and the opposite enantiomer (**7**) display higher IC_{50} values of 5.7 and 100 nM, respectively (Figure 6.2).

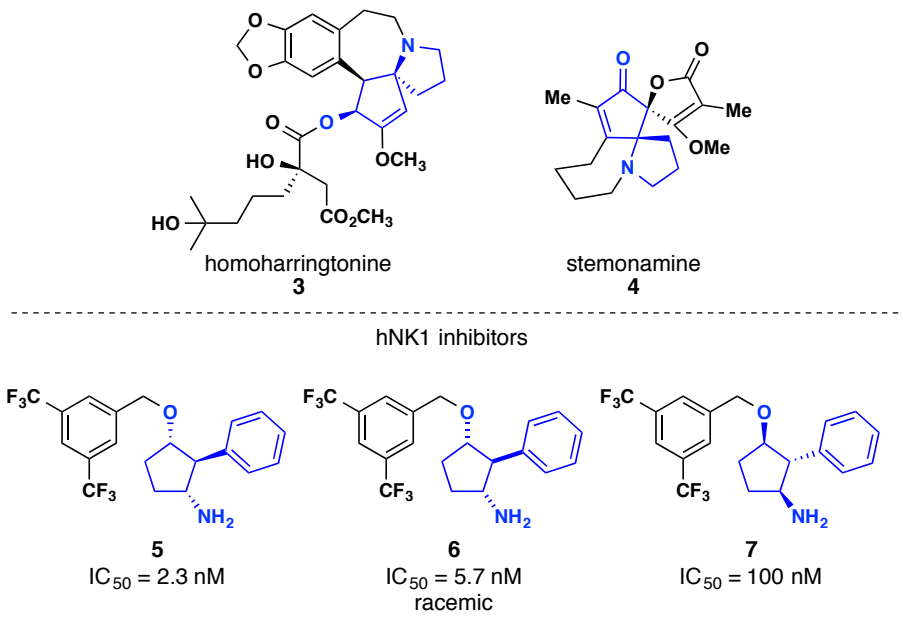


Figure 6.2. Natural products and biologically active molecules drive the need for an asymmetric aza-Piancatelli rearrangement.

Finally, an asymmetric aza-Piancatelli rearrangement is valuable from a fundamental standpoint since nothing is known yet about the interaction of chiral catalysts with these substrates or how to effect enantioinduction during the bond-forming 4π conrotatory electrocyclization poses. Our efforts to address this formidable challenge are the focus of this chapter.

6.2. The Asymmetric Nazarov Cyclization

Since there exists no example of an asymmetric Piancatelli rearrangement, we examined successful asymmetric rearrangements of its cousin, the Nazarov cyclization. Although there are a number of examples of asymmetric Nazarov cyclizations,[20,21,165] there are still many challenges associated with this transformation, and a general transformation has yet to be developed. As Alison Frontier aptly stated at the 2014 Gordon Conference on Heterocyclic compounds: "The asymmetric Nazarov cyclization is *not* a solved problem."

In general, enantioselectivity in 4π conrotatory electrocyclizations is established through selective directional conrotation in either a clockwise (cw) (**10** to **11**) or counter clockwise (ccw) (**10** to **9**) manner (Figure 6.3). This type of preferential conrotation in electrocyclizations is known as torquoselectivity, and has been studied in great detail by Houk and co-wokers.[14–16]

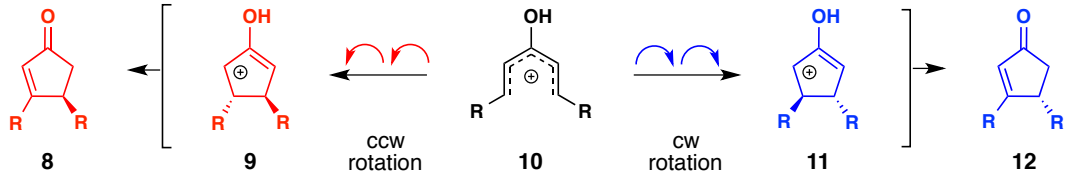


Figure 6.3. Direction of conrotation in the Nazarov cyclization controls enantioselectivity.

In the Nazarov cyclization this type of controlled directional electrocyclization to preferentially access one enantiomer over the other has been accomplished by several methods. Diastereoselective processes where an existing stereocenter guides the direction of conrotation have been described. More desirable are approaches that rely on the transfer of chirality from a chiral catalyst. To this end, both chiral Lewis acids and chiral organocatalysts have been employed. The success of these approaches has often been coupled to intelligent substrate design that focuses on designing strong interactions between the catalyst and substrate, such as two-point binding (**14**) (Figure 6.4). Notable progress and examples of the asymmetric Nazarov cyclization are described below.

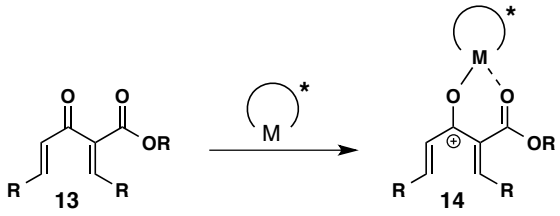
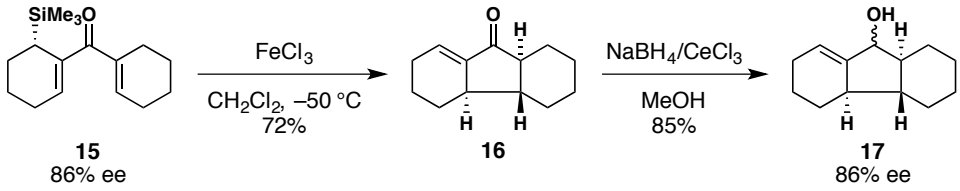


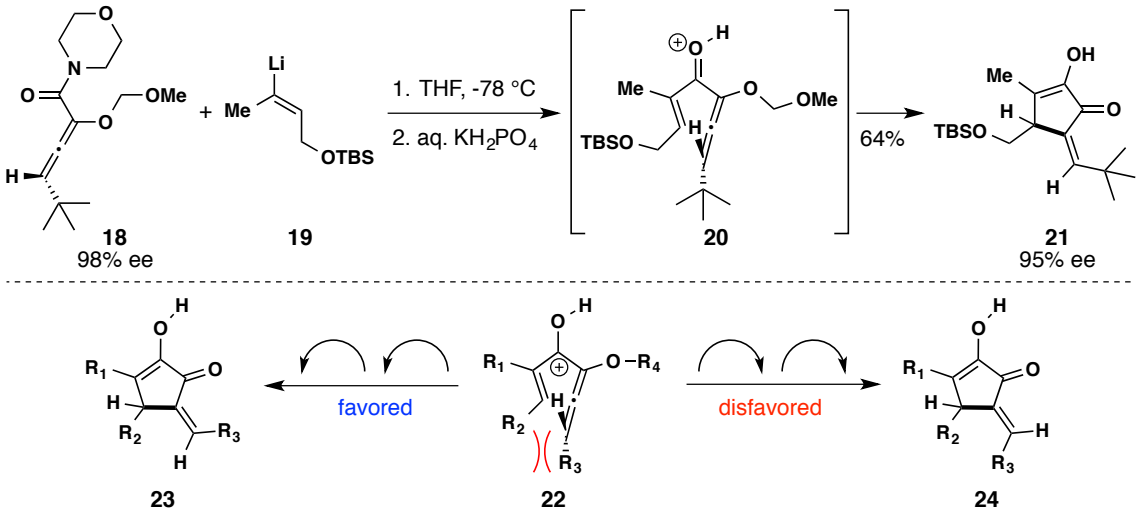
Figure 6.4. Two-point binding of a chiral catalyst to a Nazarov substrate.

Denmark and co-workers reported the first example of a torquoselective Nazarov cyclization during their studies of a silicon directed electrocyclization in 1990.[166] They found that the presence of a remote stereocenter could influence the direction of conrotation, which allowed for retention of stereochemistry from the starting material (Scheme 6.1).



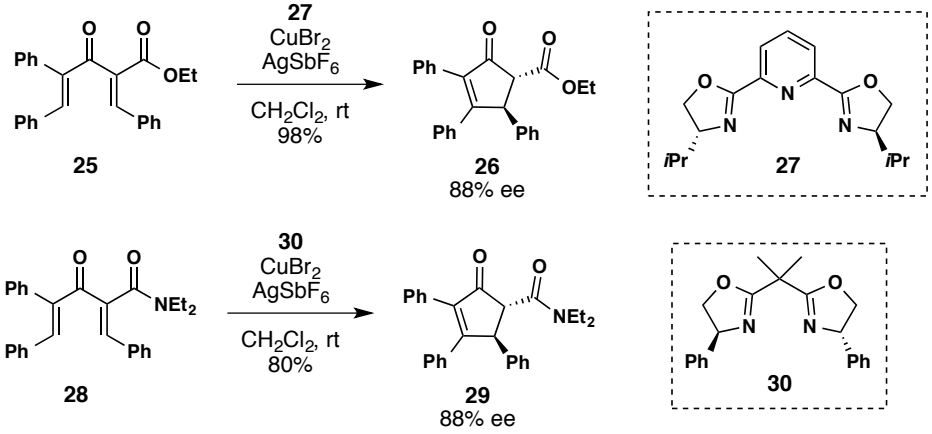
Scheme 6.1. Retention of stereochemistry in a silicon-directed Nazarov cyclization.

Tius and co-workers reported another elegant approach toward an asymmetric Nazarov cyclization, where axial chirality from an allene is transferred to the tetrahedral chirality of the Nazarov product.[167] The reaction proceeded in 65% yield with 95% chirality transfer (Scheme 6.2). The observed retention of chirality is proposed to come from a steric interaction between R_2 and R_3 that favors rotation in a counter-clockwise manner (**22** to **23**) (Scheme 6.2).



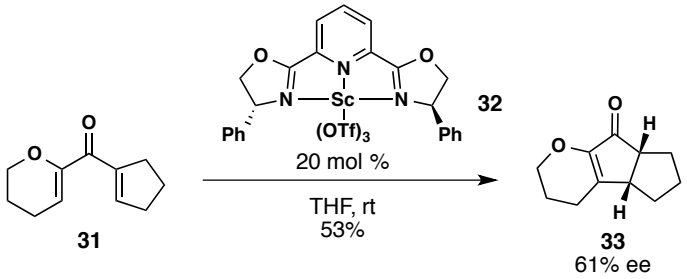
Scheme 6.2. Transfer of axial to tetrahedral chirality in the Nazarov cyclization.

Despite the value of and interest in an asymmetric Nazarov cyclization, it was not until fourteen years after Denmark's report of silicon-directed chirality transfer in the Nazarov cyclization that an asymmetric Lewis acid catalyzed variant was reported. Aggarwal and Belfield described the reaction of divinyl ketones bearing α-ester (**25**) or α-amide (**28**) groups that can coordinate to chiral copper-pyBOX and copper-BOX complexes resulting in up to 88% enantiomeric excess (ee) (Scheme 6.3).[168]



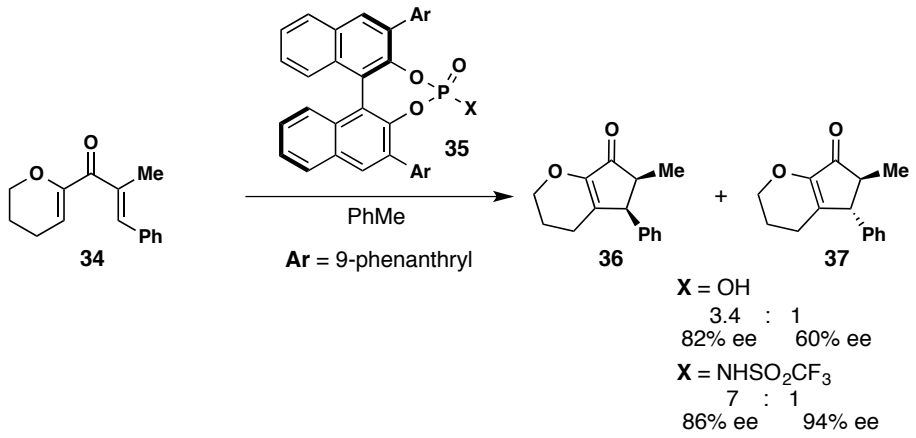
Scheme 6.3. First asymmetric Nazarov reaction with chiral Lewis acids.

Concurrently with Aggarwal's report, Trauner and co-workers described a single example of the first catalytic asymmetric Nazarov cyclization.[169] This reaction of divinyl ketone derivative (**31**) was catalyzed by a chiral pyBOX-scandium complex (**32**) and resulted in an impressive 61% ee (Scheme 6.4). The Trauner group followed up on this work with another report on enantioselective Nazarov reactions; however, the enantioselectivity in these reactions is attributed to asymmetric proton transfer rather than torquoselective cyclization (not shown).[170]



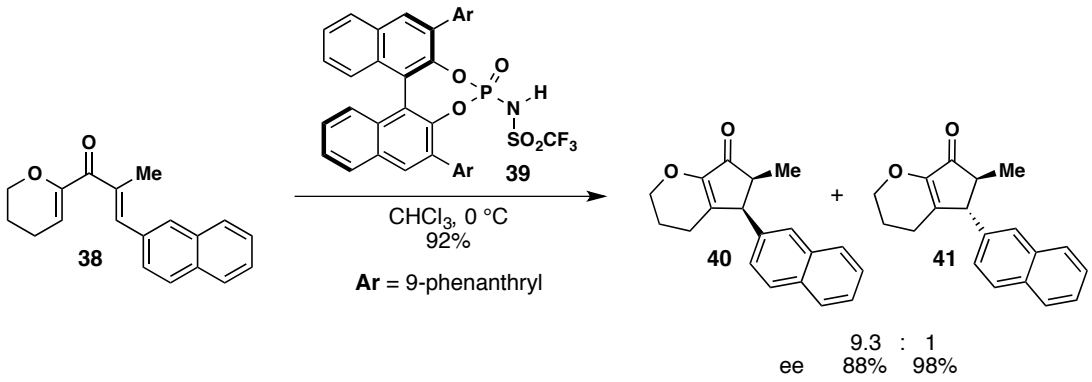
Scheme 6.4. The first catalytic asymmetric Nazarov cyclization.

The first example of an organocatalytic asymmetric Nazarov cyclization was reported by Rueping and co-workers in 2007.[171] Investigating the use of chiral Brønsted acids, they discovered that chiral phosphoric acids and *N*-triflyl phosphoramides catalyzed the electrocyclization in a torquoselective manner with up to 94% enantioselectivity (Scheme 6.5).



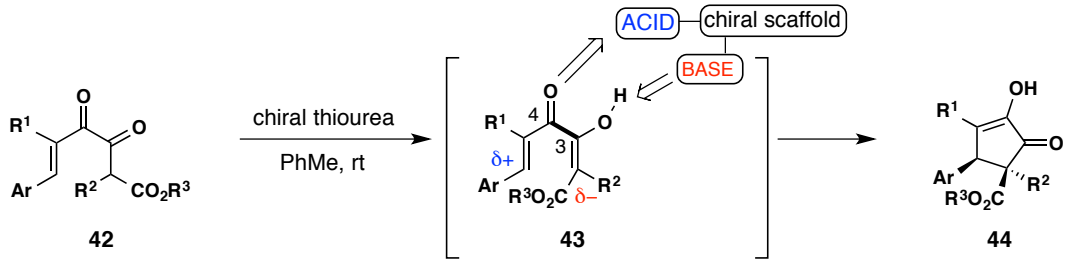
Scheme 6.5. First organocatalyzed enantioselective Nazarov cyclization.

Best results were achieved with 9-phenanthryl substituted *N*-triflyl phosphoramide **39** in $CHCl_3$ at 0 °C, yielding the desired cyclopentenones **40** and **41** in excellent yield and up to 98% ee (Scheme 6.6).



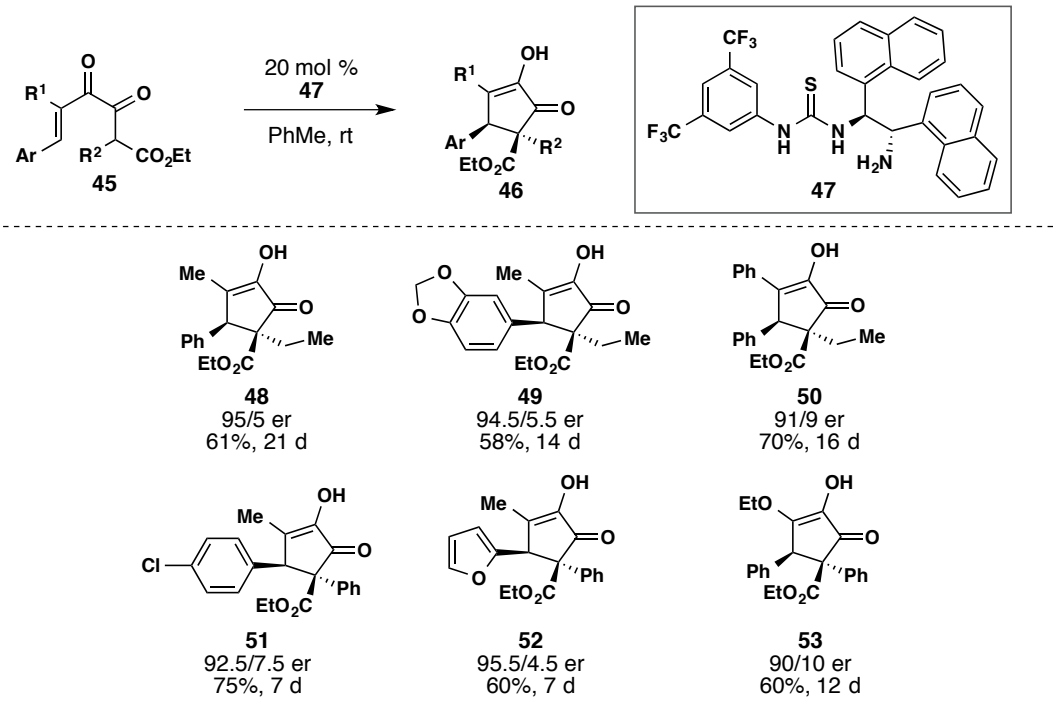
Scheme 6.6. Results with optimized reaction conditions for the chiral *N*-triflyl phosphoramide catalyzed Nazarov cyclization.

Tius and co-workers developed an elegant strategy for an organocatalytic asymmetric Nazarov cyclization with chiral thiourea catalysts.[172] The method involved the synthesis of strategically designed diketoesters (**42**) capable of reversibly binding to bifunctional chiral catalysts (Scheme 6.7). Two-point binding to the catalyst would yield a polarized intermediate (**43**) poised for the bond-forming electrocyclization.



Scheme 6.7. Strategy for enantioinduction using a bifunctional chiral thiourea catalyst.

This method worked well in terms of chirality transfer and was applied to the synthesis of a variety of densely functionalized cyclopentenones (**48**-**53**) bearing chiral all-carbon quaternary centers (Scheme 6.8). However, the strategy is by no means general and drawbacks include slow reaction times (up to 21 days) due to product inhibition, and a limitation to specially synthesized substrates and catalysts.



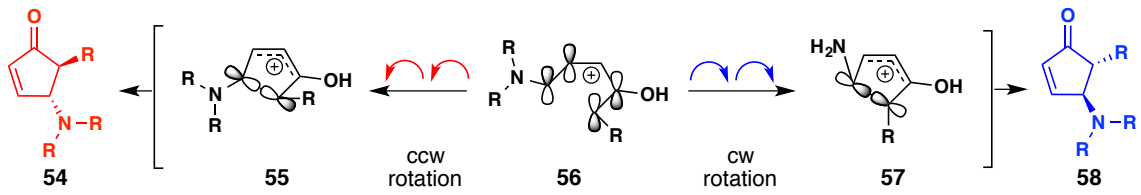
Scheme 6.8. Select scope of the chiral thiourea catalyzed Nazarov cyclization.

The select examples discussed above represent a variety of strategies that have been successfully applied towards developing asymmetric Nazarov cyclizations. The strategies include chirality transfer, catalytic and stoichiometric reactions with chiral Lewis acid catalysts, as well as cyclizations with chiral organocatalysts. A commonality among the approaches presented is the presence of the stereodirecting group in close proximity to the location of bond formation. Additional examples can be found in a recent review by Tius and co-workers.[165]

6.3. Toward an Asymmetric Aza-Piancatelli Rearrangement.

Equipped with a knowledge of successful enantioselective Nazarov cyclizations, we began our investigations of an asymmetric aza-Piancatelli rearrangement. We hypothesized that the induction of asymmetry needs to come from preferential torquoselective cyclization in either a clockwise (cw) (**56** to **57**) or counter-clockwise (ccw) (**56** to **55**) direction to

provide preferential access to either enantiomer (Scheme 6.9). In addition, we knew that success in this area would likely result from the presence of the chiral unit in close proximity to the bond-forming event.



Scheme 6.9. Torquoselectivity will enable preferential access to enantiomers.

Unlike the Nazarov cyclization, where the catalyst is responsible for the formation of the carbocation, and thus is automatically either bound to, or in close proximity of the pentadienyl cation, little is known about the role of the catalyst after formation of the oxocarbenium ion in the aza-Piancatelli rearrangement. As such, we considered four different approaches to the asymmetric aza-Piancatelli rearrangement (Figure 6.5). In theory the simplest approach would be the use of chiral amines (Figure 6.5, **A**). Chiral secondary amines are abundant, but unfortunately our studies have shown that we are limited to a small pKa range of nucleophiles for the rearrangement (see Chapter 4). Chiral anilines can be prepared, but the chiral centers are generally far removed from the bond-forming process, making chirality transfer unlikely. We also envisioned the design of furylcarbinols bearing a chiral auxiliary (Figure 6.1, **B**), but decided not to pursue that direction since chirality transfer from a catalyst is preferable in terms of broad applicability. Finally we envisioned the use of either chiral Lewis acids or chiral organocatalysts (Figure 6.5, **C** and **D**). These two strategies rely on a strong interaction between the catalyst and substrate during the bond-forming event for chirality transfer. Despite the lack of information about the fate of the catalyst in the aza-Piancatelli rearrangement, we decided to pursue these two strategies, confident that we would identify a catalyst that interacts with the pentadienyl intermediate.

Ideally, this interaction would proceed through the coordination or tight ion pair of the catalyst with the amine substituent or the OH group at the 4-position of the pentadienyl cation.

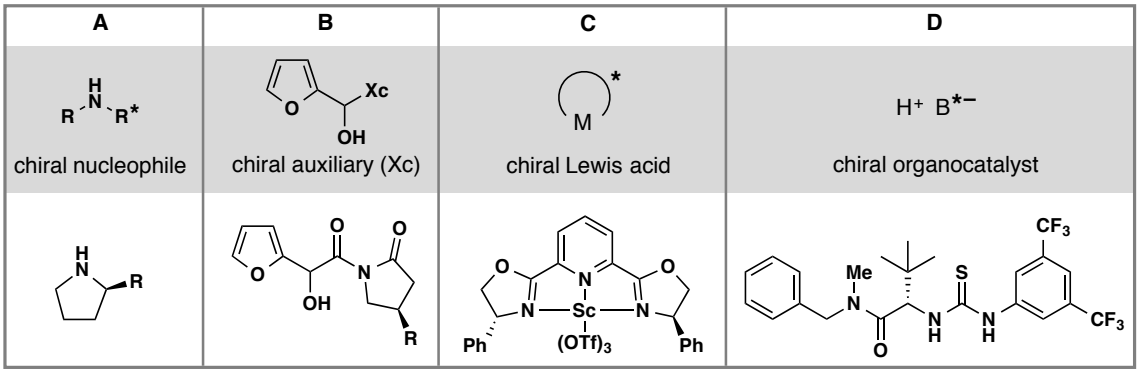
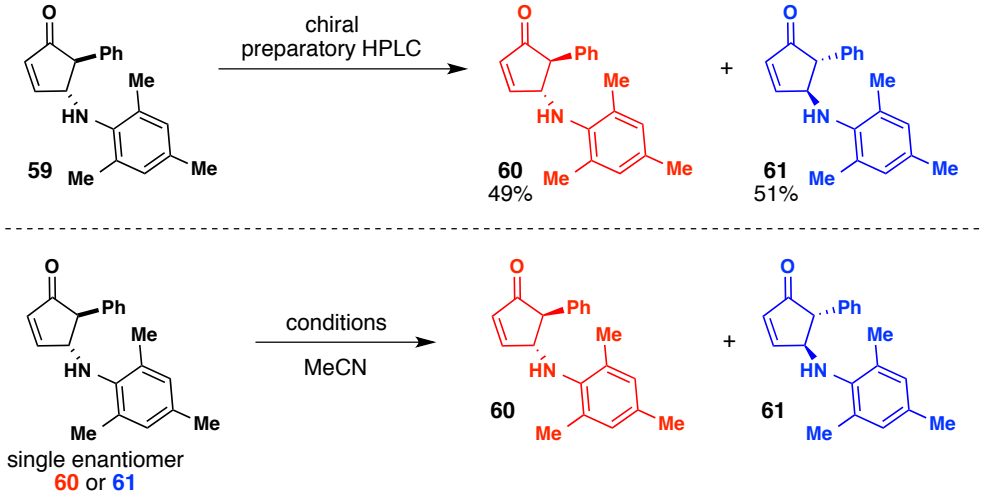


Figure 6.5. Four possible approaches toward inducing enantioselectivity in the aza-Piancatelli rearrangement.

Before setting up reactions with precious chiral catalysts, we studied the reversibility of the reaction to ensure that enantioselectivity established by torquoselective cyclization would not be eroded by another process. To accomplish this, we separated the enantiomers of **59** using chiral preparatory HPLC, and subjected the single enantiomers to a variety of reaction conditions (Table 6.1). We found that there is no change in enantiopurity in the presence of dysprosium at rt (entry 1), but that this enantiopurity is eroded under standard reaction conditions with $Dy(OTf)_3$ at 80 °C over time (Table 6.1, entries 2 and 3) and applies to either enantiomer. Finally, in the absence of $Dy(OTf)_3$, heating at 80 °C does not erode the enantiopurity (entry 5). Based on these results, we focused our efforts on reactions at room temperature to avoid loss of the established enantioselectivity over the course of the reaction.

Table 6.1. Studies on the reversibility of the aza-Piancatelli rearrangement.[a]



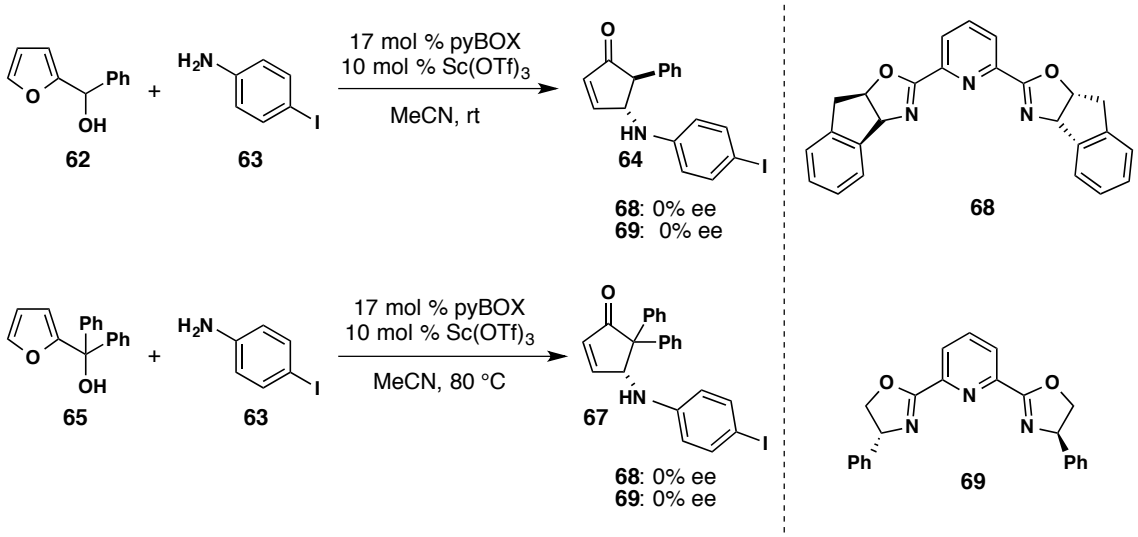
Entry	Enantiomer	Catalyst (5 mol %)	Temp [°C]	Time	60:61[b]
1	**60**	$Dy(OTf)_3$	23	17 h	100:0
2	**60**	$Dy(OTf)_3$	80	30 min	73:27
3	**60**	$Dy(OTf)_3$	80	4 h	49:51
4	**61**	$Dy(OTf)_3$	80	4 h	49:51
5	**61**	--	80	4 h	0:100

[a] The absolute configuration of the isomers has not been determined. The depicted configuration was arbitrarily assigned. [b] Ratios were determined by analytical HPLC.

6.3.1. Chiral Lewis Acid Catalysis

Our first attempts at an asymmetric aza-Piancatelli rearrangement were based on reactions catalyzed by $RE(OTf)_3$ in combination with chiral ligands, including reactions inspired by Trauner's success with pyBOX-scandium complexes.[169,170] We chose to perform all reactions at room temperature based on the results in Table 6.1. One general drawback of the aza-Piancatelli rearrangement that we were aware of from the start is that the reaction proceeds quickly and cleanly in polar solvents, but is sluggish and results in formation of substitution products in nonpolar solvents. This is unfortunate for an asymmetric reaction where chemists often rely on nonpolar solvents to encourage strong interactions between polar substrates and catalysts.

To our disappointment, reactions with scandium-pyBOX complexes resulted in no enantioselectivity (Scheme 6.10). The use of bis-phenylfurylcarbinol **65** and chiral scandium-pyBOX were performed at elevated temperatures since the stereocenter cannot be eroded, but unfortunately these reactions also resulted in no enantioselectivity (Scheme 6.10).



Scheme 6.10. Aza-Piancatelli rearrangements with scandium pyBOX complexes.

Interestingly, a recent result showed that the addition of 5 mol % sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF, **70**) to the scandium-pyBOX reaction of phenylfurylcarbinol **62** and *p*-iodoaniline in toluene results in 10% ee (Figure 6.6).[173] Although this is an incremental advance, it does show that there is potential for a chiral Lewis-acid catalyzed aza-Piancatelli rearrangement.

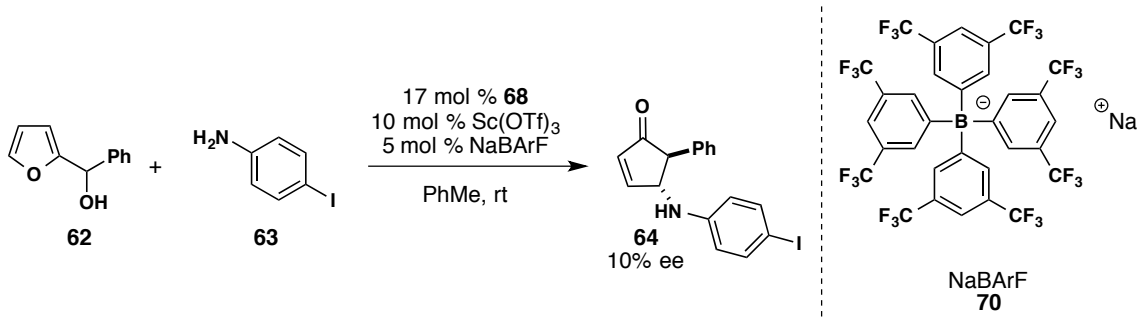
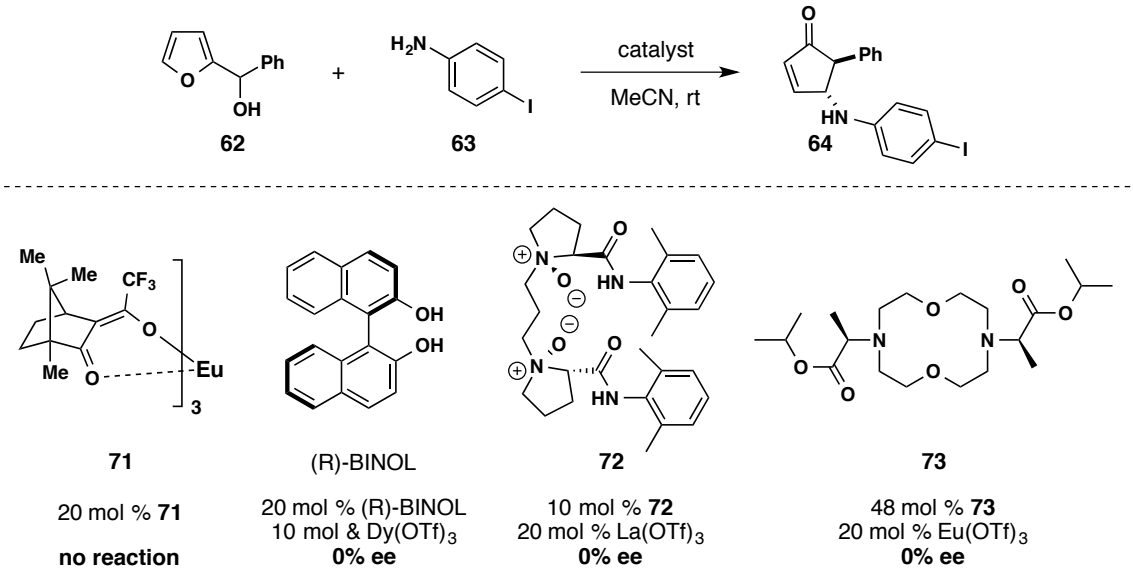


Figure 6.6. Reaction with NaBArF additive.

We examined a number of other $RE(OTf)_3$ based chiral catalyst systems with no success (Scheme 6.11). Commercially available europium shift reagent **71**, which could potentially act as a Lewis acid, did not catalyze the aza-Piancatelli rearrangement. Reactions with a (R)-BINOL and $Dy(OTf)_3$ did result in product formation, but unfortunately no enantioinduction was observed. Enantioinduction was also absent when using Kobayashi's conditions with BINOL, $Yb(OTf)_3$ and Hünig's base (not pictured).[174] The same goes for a reaction catalyzed by a lanthanum-*N*, *N'*-dioxide complex **72**,[175,176] as well as a europium complex with Matthew Allen's ligand **73**.[177]

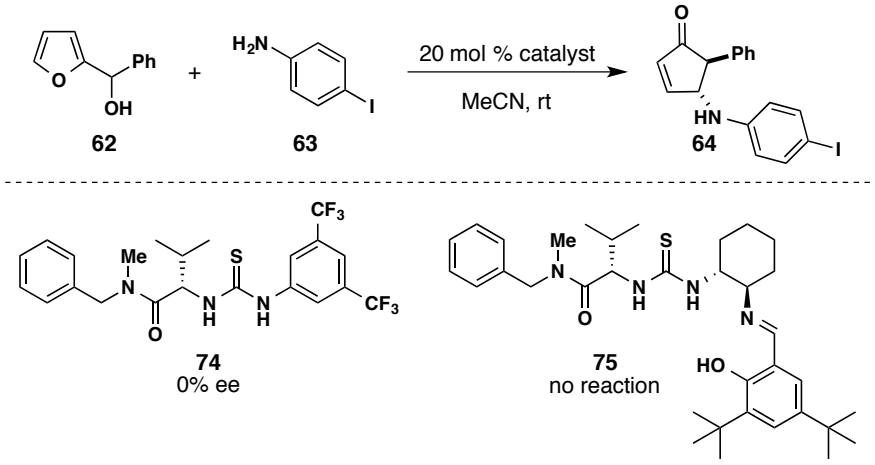


Scheme 6.11. Aza-Piancatelli rearrangement with a variety of chiral $RE(OTf)_3$ complexes.

6.3.2. Chiral Organocatalysis

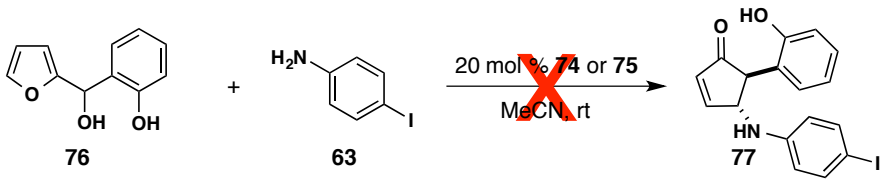
With little success using chiral Lewis acid complexes for the asymmetric aza-Piancatelli, we turned to organocatalysts inspired by Tius and co-worker's work.[172] We chose to examine both chiral thiourea, as well as chiral cinchona alkaloid catalysts, which could potentially transfer chirality to the electrocyclization through hydrogen-bonding interactions or through a tight ion pair.

As with the chiral Lewis acid complexes, reactions with chiral thiorueas **74** and **75** did not result in an asymmetric transformation (Scheme 6.12). In fact, addition of **75** did not result in any reaction. Addition of 20 mol % $Dy(OTf)_3$ did result in product formation, but again without any enantioselectivity.



Scheme 6.12. Chiral thiourea catalyzed aza-Piancatelli rearrangements.

Speculating that a second binding site might be necessary for successful transfer of chirality from the catalyst to the substrate,[172] we synthesized furylcarbinol **76** with a phenolic alcohol that could serve as a secondary binding site. To our disappointment, no reaction was observed when using either thiourea catalyst (Scheme 6.13), despite the success of the transformation utilizing standard $Dy(OTf)_3$ reaction conditions.



Scheme 6.13. A second binding site shuts down the aza-Piancatelli rearrangement with chiral thiourea catalysts.

Chiral cinchona alkaloids **78** and **79** were also tested, but resulted in either no reaction or no enantioselectivity even if used in conjunction with $Dy(OTf)_3$ (Figure 6.7).

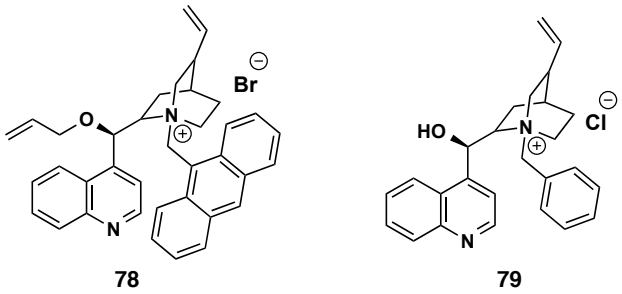


Figure 6.7. Cinchona alkaloids are ineffective chiral catalysts for the aza-Piancatelli rearrangement.

6.3.3. Chiral Phosphoric Acid Catalysis

Disappointed with the lack of success thus far, we finally turned to chiral Brønsted acid catalysis as a means for torquoselective cyclization in the aza-Piancatelli rearrangement. Although (–)-camphorsulfonic acid (pKA 1.2) readily catalyzes the aza-Piancatelli rearrangement, no enantioselectivity was observed. With Rueping's organocatalytic asymmetric Nazarov cyclization in mind,[171] we became interested in exploring chiral phosphoric acids. The pKas of chiral phosphoric acids and derivatives vary depending on substituents and the choice of solvent, but generally range from 6 to -4,[178,179] leading us to believe that the more acidic cases could catalyze the aza-Piancatelli rearrangement.

Summarized in Table 6.2 are the results of the reaction with a variety of chiral phosphoric acids in MeCN and PhMe. While (R)-VAPOL was quite ineffective as a catalyst, we did detect 4% ee (Table 6.2, entry 1). We were delighted to find that Benjamin List's bulky (R)-TRIP would not only catalyze the rearrangement,[180,181] but also resulted in an impressive and unprecedented 46% ee in MeCN and 49% ee in $MeNO_2$ at rt (Table 6.2, entries 2 and 3). These results represent the very first examples of an asymmetric aza-Piancatelli rearrangement with reasonable selectivity. HPLC traces of the racemic dysprosium catalyzed reaction and the reaction with 20 mol % (R)-TRIP resulting in 46% ee (27:73 enantiomeric ratio) are shown in Figure 6.8.

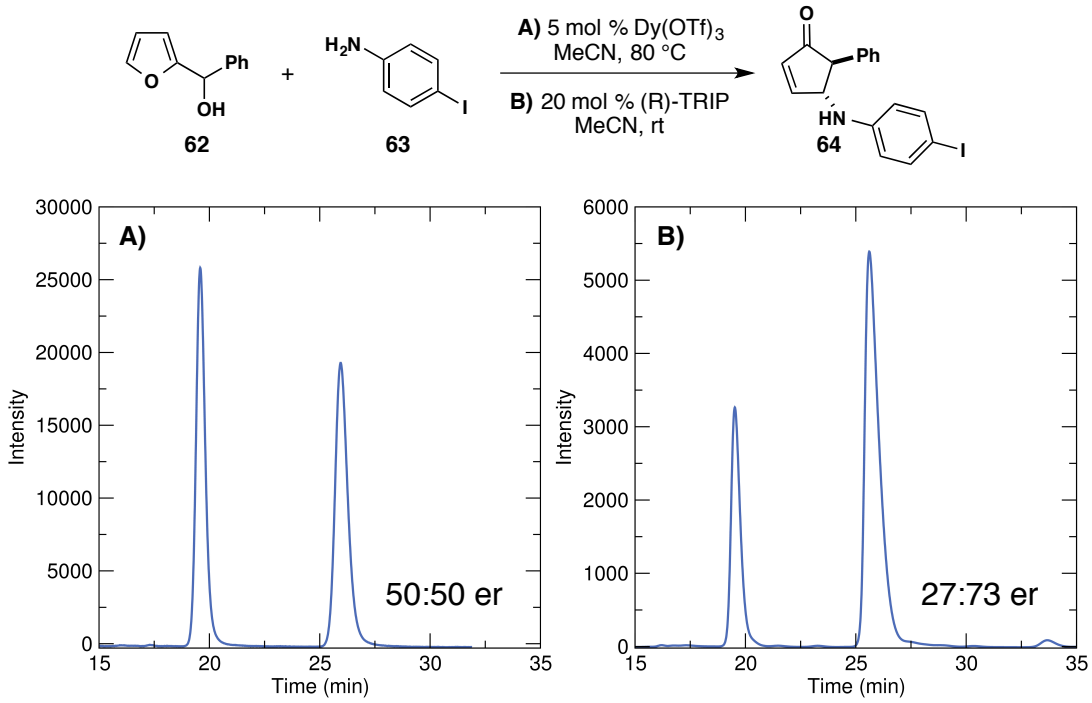
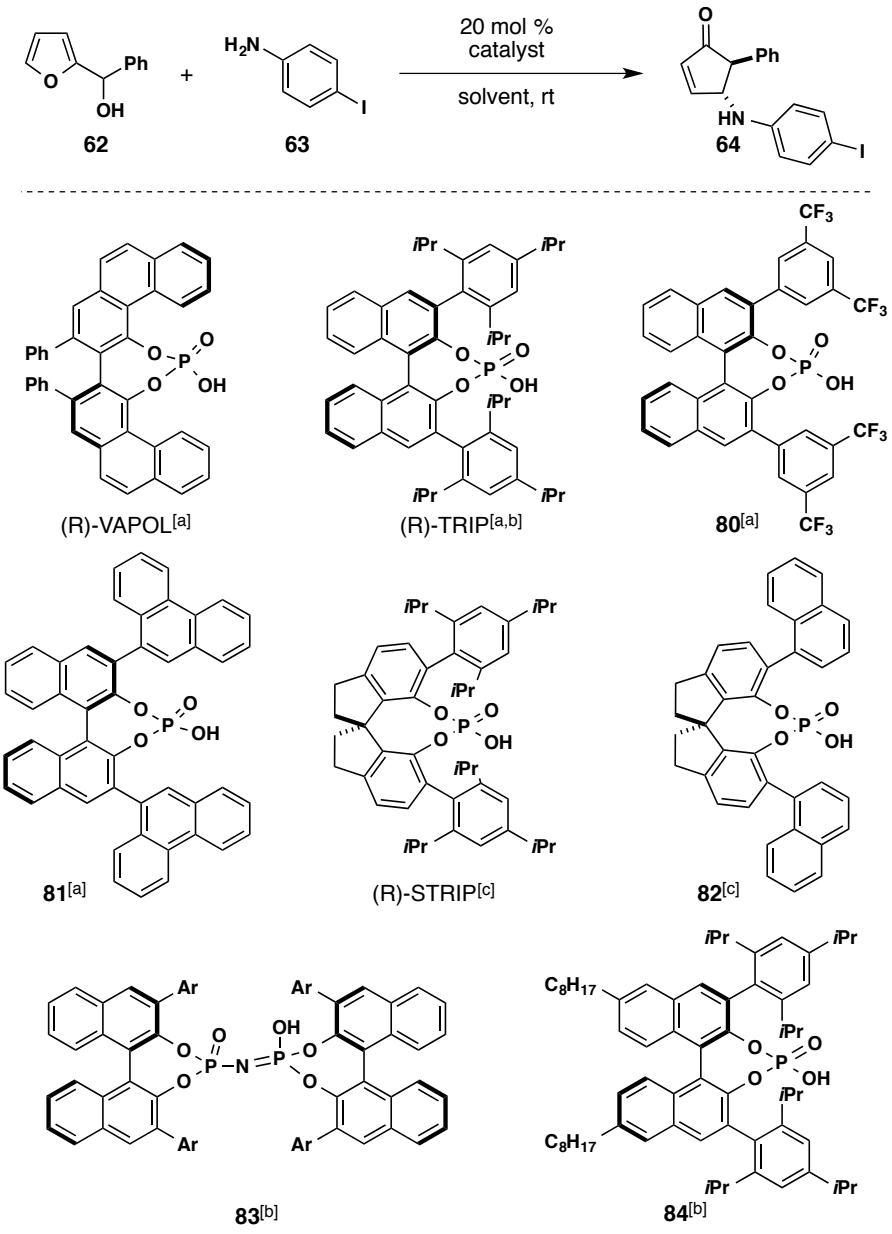


Figure 6.8. HPLC traces of the A) racemic and B) enantioselective aza-Piancatelli rearrangement.

Increasing the amount of chiral phosphoric acid to a full equivalent did not increase the enantioselectivity or rate of the reaction. It should be noted that reactions with (R)-TRIP and other chiral phosphoric acids were extremely slow and often did not go to completion. We

decided to initially focus mainly on enantioselectivity rather than rate enhancement, and therefore do not report yields of reactions.

Table 6.2. Aza-Piancatelli rearrangement catalyzed by chiral phosphoric acids.



[a] Catalyst donated by Sigma-Aldrich. [b] Catalyst prepared in the Read de Alaniz lab. [c] Catalyst donated by the Antilla group.

Entry	Catalyst	Solvent	% ee
1	(R)-VAPOL	MeCN	4
2	**(R)-TRIP**	**MeCN**	**46**
3	**(R)-TRIP**	**$MeNO_2$**	**49**
4	(R)-TRIP	PhMe	29
5	(R)-TRIP	CH_2Cl_2	19
6	**80**	MeCN	5
7	**80**	PhMe	34
8	**81**	MeCN	9
9	**81**	PhMe	12
10	(R)-STRIP	MeCN	12
11	**82**	MeCN	5
12	**83**	MeCN	no reaction
13	**84**	MeCN	36

Although there is some precedent for successful enantioinduction with chiral phosphoric acids in MeCN,[182] best results are usually achieved in nonpolar solvents such as toluene. We found that the asymmetric aza-Piancatelli is fairly unusual in that reactions with (R)-TRIP in toluene or CH_2Cl_2 result in lower selectivity compared to polar MeCN and $MeNO_2$ (Table 6.2, entries 4 and 5 vs entries 2 and 3).[182] Interestingly however, trifluoromethyl-substituted chiral phosphoric acid **80** followed a more traditional path, resulting in increased reaction times with low enantioselectivity in MeCN but good selectivity in toluene (Table 6.2, entries 6 and 7). The increased reaction rates can be attributed to a lower pKa value of **80** (pKa = 2.63) compared to that of (R)-TRIP (pKa = 3.18).[179] Use of chiral phosphoric acid **81** resulted in only 9 and 12% ee in MeCN and toluene, respectively (Table 6.2, entries 8 and 9), and was not further pursued.

Thanks to a generous donation by Professor Jon Antilla at the University of South Florida, we were also able to test reactions with chiral phosphoric acids based on the 1,1'-spirobiindane backbone, including (R)-STRIP and **82**.[183] We hoped that the more rigid chiral pocket might generate an increase in enantioselectivity, but unfortunately the chiral pocket

must be too small for the aza-Piancatelli rearrangement, and a decrease in enantioselectivity was observed for both (R)-STRIP and **82** (Table 6.2, entries 10 and 11). Along the same lines, List reported the synthesis of the dimeric imidophosphoric acid **83**,[184] which we synthesized, but found that it did not catalyze the reaction (Table 6.2, entry 12). One challenge we faced with the use of chiral phosphoric acids was solubility. Often heterogenic mixtures formed and it was difficult to determine if this affected our enantioselectivity. To probe this question, we sought to use more lipophilic variants of the catalyst. Lipophilic (R)-TRIP derivative **84** was prepared by undergraduate researcher Aurora Ginzburg,[185] but despite the alkyl chains increasing the solubility of the catalyst in MeCN, the enantioselectivity was not positively affected (Table 6.2, entry 13).

We hypothesized that the source of the observed enantioselectivity comes from an interaction between the chiral phosphoric acid and the pentadienyl cation in one of two ways (Figure 6.9). The chiral phosphoric acid could serve as a chiral counterion that interacts either with the amine (**85**) or, alternatively, interacts with the alcohol on the other side (**86**). Alternatively, one could imagine the presence of π-stacking interactions between the chiral phosphoric acid and the aryl groups (not depicted).

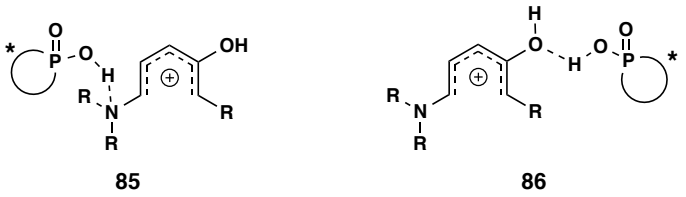


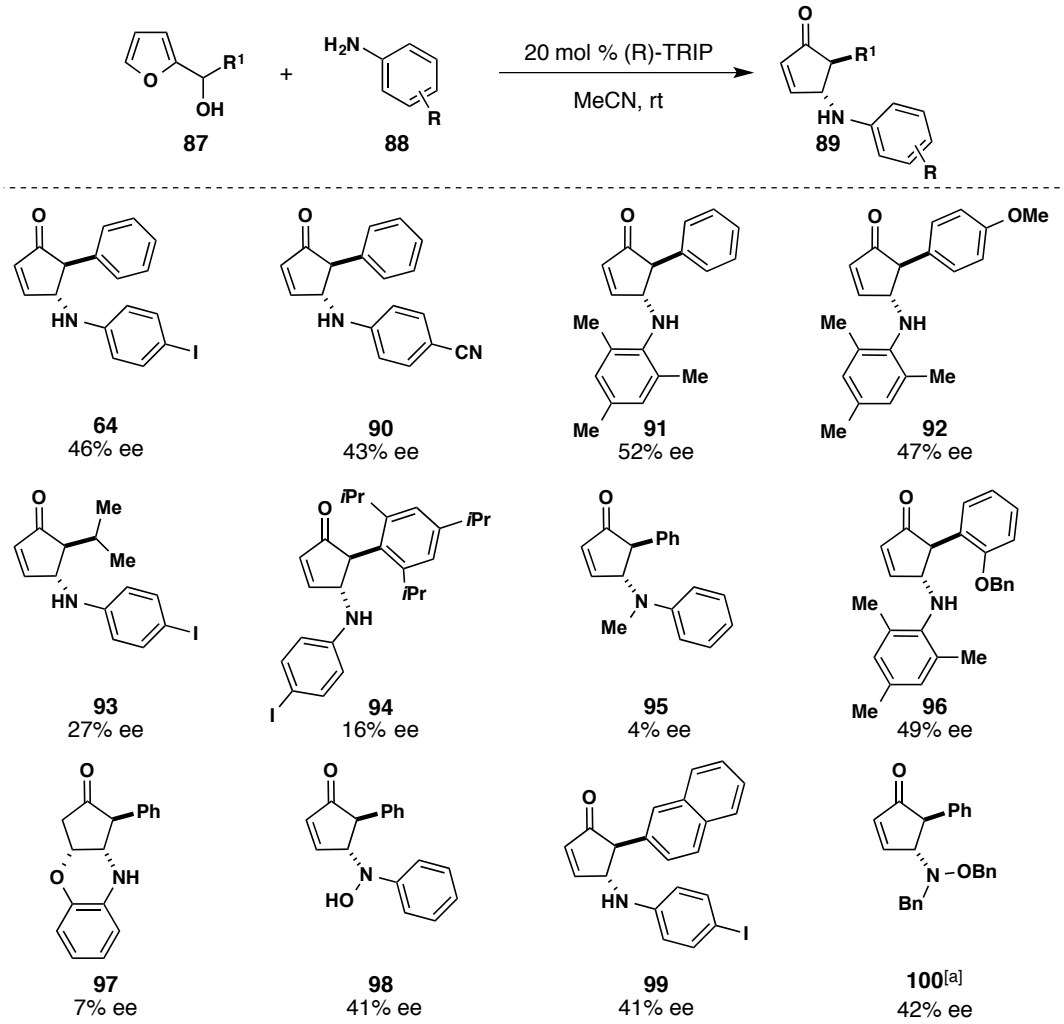
Figure 6.9. Proposed points of catalyst-substrate interactions.

We hoped to hone in on the catalyst-substrate interaction, and perhaps positively influence enantioselectivity, by examining the scope of the rearrangement with our best catalyst, (R)-TRIP. If successful, this would allow us to rationally design new catalysts. The results of this investigation are summarized in Table 6.3.

The (R)-TRIP catalyzed aza-Piancatelli rearrangement with *p*-cyanoaniline (**90**) resulted in similar enantioselectivity as *p*-iodoaniline (**64**) while sterically bulky 2,4,6-trimethylaniline results in cyclopentenone **91** with an impressive 52% ee. However, the formation of **91** is extremely sluggish and the reaction did not go to completion over the course of a month. Switching from furylcarbinol **62** to its more activated acylated equivalent did speed the reaction up a bit, but resulted in only 45% ee (not depicted). Employing more activated *p*-methoxy substituted furylcarbinol, the reaction was significantly faster, but resulted in a small drop in enantioselectivity (**92**). The use of an alkyl substituent or sterically bulky triisopropylphenyl furylcarbinol resulted in a marked drop in enantioselectivity down to 27% and 16%, respectively (**93** and **94**).

In an attempt to further our understanding of where the chiral catalyst sits during the stereodetermining event (Figure 6.9), we examined a number of substrates. Use of secondary *N*-methyl aniline resulted in nearly complete erosion of selectivity (**95**). The presence of a potential secondary binding point on the R^1 substituent had no effect on the enantioselectivity compared to a simple aryl group (**96** compared to **91**). In an effort to trap the stereochemical configuration after the reaction, we performed the reaction with 2-aminophenol, where a Michael addition into the enone follows the rearrangement.[186] Unfortunately, the reaction with 2-aminophenol resulted in greatly reduced enantioselectivity (**97**). It should be noted that this reaction does proceed through an aza-Piancatelli first, since phenols do not participate in the Piancatelli rearrangement.

Table 6.3. Scope of the aza-Piancatelli rearrangement with (R)-TRIP.

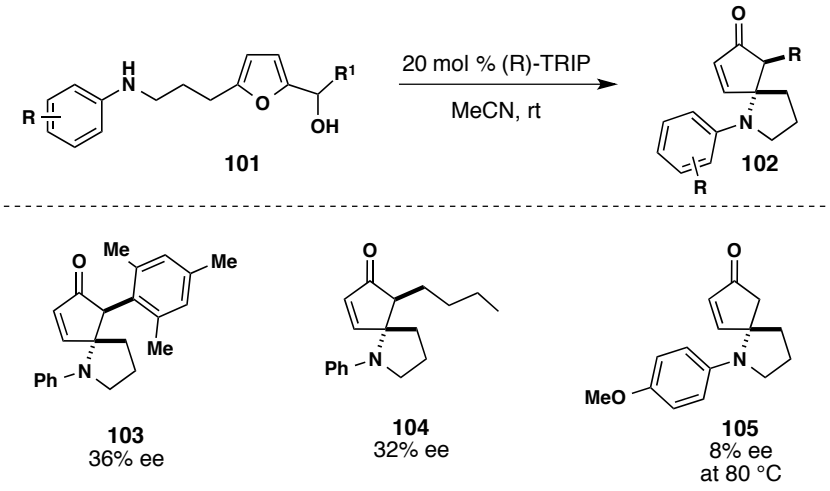


[a] The reaction was performed in $MeNO_2$.

N-Phenylhydroxylamine (**98**) and *N*,*O*-dibenzylhydroxylamine (**100**) performed similarly to anilines, showing no improvement due to the presence of potential binding points. Finally, we proposed that the presence of an R^1 group capable of π-stacking, such as naphthalene, may improve the interaction with (R)-TRIP and result in greater enantioselectivity based on a report by Jacobsen with chiral thiourea catalysts,[187] but again we observed no such effect (**99**). Reactions with donor-acceptor cyclopropane substituted furans were not catalyzed by chiral phosphoric acids.[140]

Proposing that a tethered nucleophile may simplify the reaction and thus lead to an increase in enantioselectivity, we tested the (R)-TRIP catalyzed intramolecular aza-Piancatelli rearrangement. Although the reactions were catalyzed, enantioselectivities in the intramolecular aza-Piancatelli rearrangement were lower than those with an external nucleophile (Table 6.4, **103-105**).

Table 6.4. (R)-TRIP catalyzed intramolecular aza-Piancatelli rearrangement.

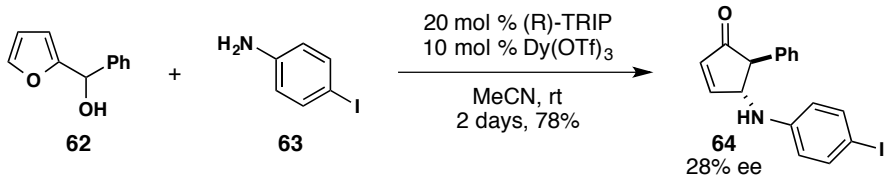


At this point, we had examined a variety of chiral phosphoric acids and identified (R)-TRIP as the best contender and had also studied the scope of the aza-Piancatelli rearrangement and determined that (R)-TRIP is an excellent catalyst effecting up to 52% ee. However, our attempts at influencing the enantioselectivity of the reaction via substrate control did not further our understanding of the binding mode of the catalyst and the origin of torquoselectivity that leads to the observed enantiomeric excess. Since the synthesis of chiral phosphoric acids is fairly involved and modification of the BINOL backbone occurs early on in the synthesis, we decided to focus on examining additives for the (R)-TRIP catalyzed aza-Piancatelli rearrangement.

6.3.4. Additives in the Chiral Phosphoric Acid Catalyzed Aza-Piancatelli Rearrangement

The literature on chiral phosphoric acids is full of examples of increased reactivity and enantioselectivity in the presence of a wide range of additives, and we decided to explore some of these options in the search for increased reactivity and enantioselectivity. Reactions with (R)-TRIP in MeCN often take weeks to go to completion, but proceed faster in $MeNO_2$ (8 days; Table 6.2, entry 3). Obviously faster reaction times are desired, and we hoped that additives might provide the necessary increased activation as well as enantioselectivity. Our first forays into additives started with the addition of metal catalysts.

Reactions that pair chiral phosphoric acid catalysts and rare earth triflates have been reported by Inanaga and co-workers for enantioselective HDA reactions,[188] leading us to evaluate a combination of (R)-TRIP and $Dy(OTf)_3$. Our hope was that dysprosium would give the added activation boost while allowing the chiral phosphoric acid to direct the stereodetermining event. Although it was pleasing to find that the reaction proceeded much faster with $Dy(OTf)_3$ as an additive, the enantioselectivity suffered (Scheme 6.14).

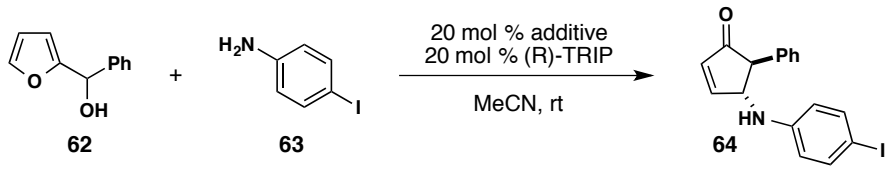


Scheme 6.14. (R)-TRIP catalyzed reaction with dysprosium additive.

Other chiral phosphoric acid-metal catalyst systems have been reported, and we chose to test the aza-Piancatelli reaction with some additives that have been shown to increase enantioselectivity, including: MgF_2,[189] $CuCl_2$,[190] $Cu(OTf)_2$, $(PPh_3)AuCl$[191,192] and $ZnBr_2$. While MgF_2 had no effect on the enantioselectivity or rate of the reaction (Table 6.5, entry

1), reactions with copper, gold and zinc additives resulted in much lower selectivity but increased reaction rates (Table 6.5, entries 2-4).

Table 6.5. Asymmetric aza-Piancatelli rearrangement with metal additives.

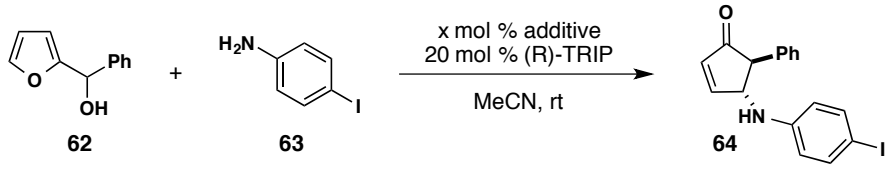


Entry	Additive	Time[a]	Yield (%)	% ee
1	MgF_2	22 d	--	44
2	$CuCl_2$	1 d	40	39
3	$Cu(OTf)_2$	10+ d	82	27
4[b]	$(PPh_3)AuCl$	4 d	21	16
5	$ZnBr_2$	1 d	91	27

[a] The reaction with (R)-TRIP without additives does not go to completion in 20 days. [b] Reaction performed in toluene.

With no observed enhanced enantioselectivity using metal additives, we next turned to the addition of acid or base to the reaction as summarized in Table 6.6. As may be expected based on our earlier control experiments with triflic acid (Chapter 2, Table 2.1), addition of KO*t*Bu shuts down the reaction completely (Table 6.6, entry 1). Surprisingly, some product formed in the presence of $NaHCO_3$, albeit with 5% ee (Table 6.6, entry 2). Basic alumina, on the other hand had no effect on the (R)-TRIP catalyzed reaction in terms of selectivity (Table 6.6, entry 3). Addition of acetic acid, which does not catalyze the reaction itself (Chapter 2, Table 2.1), had no effect on the reaction, resulting in the usual 45% ee (Table 6.6, entry 4). Addition of 20 mol % hexafluoroisopropanol (HFIP), which might increase the ability of the pentadienyl cation and chiral phosphoric acid to interact through strong hydrogen bonds, also did not affect the enantioselectivity of the reaction (Table 6.6, entry 5).

Table 6.6. Effect of basic and acidic additives on the (R)-TRIP catalyzed aza-Piancatelli rearrangement.

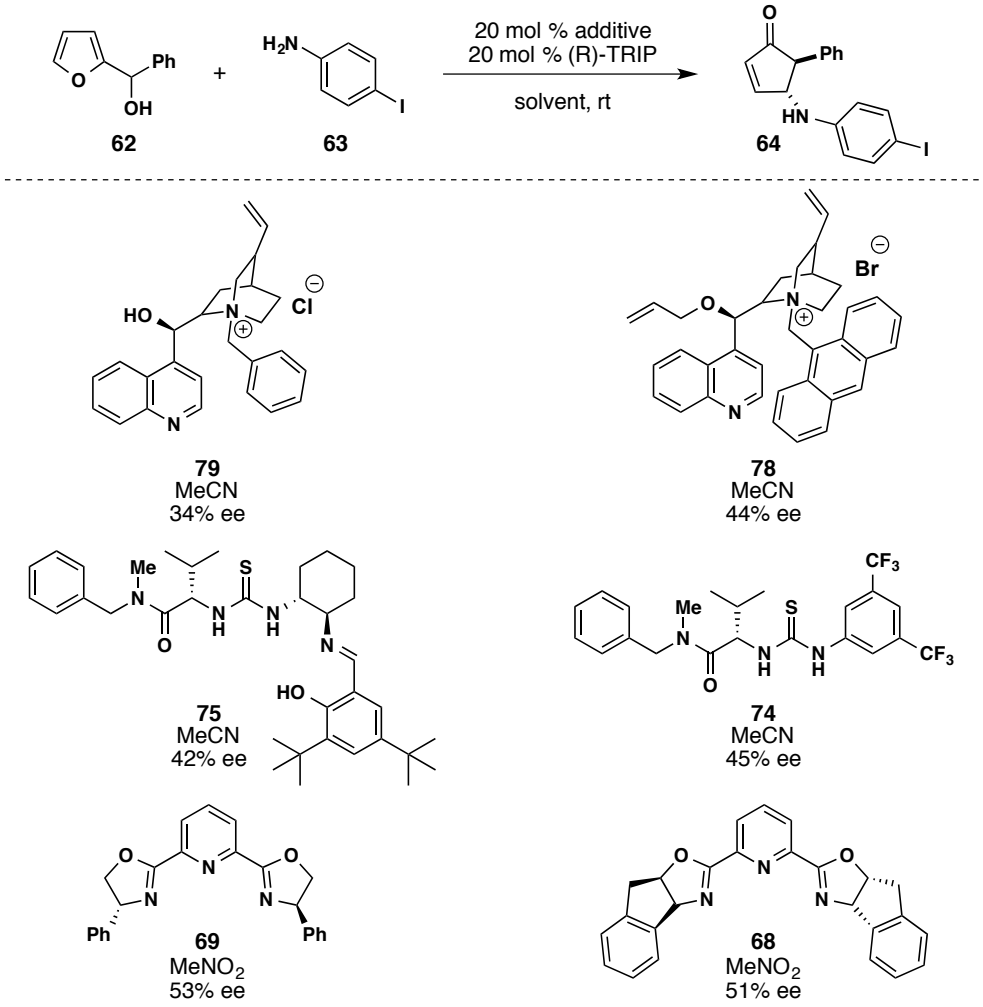


Entry	Additive	x	% ee
1	KO*t*-Bu	100	no reaction
2	$NaHCO_3$	100	5
3[a]	basic alumina	600	44
4	AcOH	15	45
5	HFIP	20	47

[a] One small scoop, equal to approximately 10 mg Al_2O_3 was added.

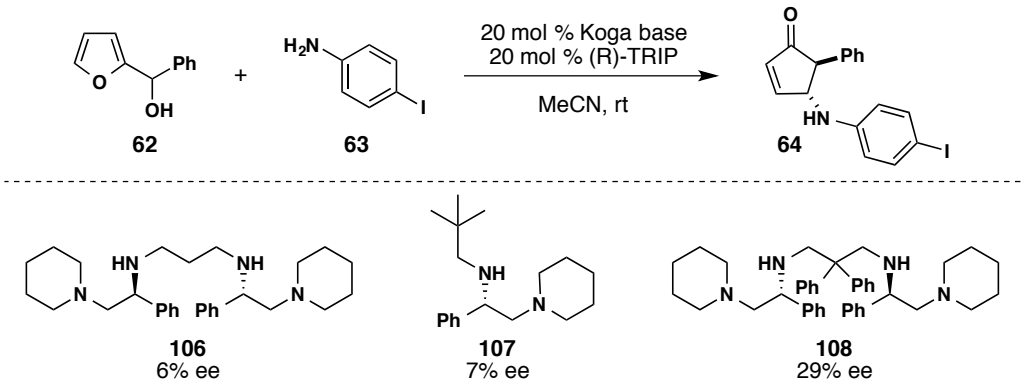
Steering away from these basic additives, we entered the arena of chiral additives. Combinations of chiral phosphoric acids with chiral cinchona alkaloids have resulted in excellent selectivity in double Michael addition reactions.[193] Reactions of (R)-TRIP with **79** and **78** led to 34 and 44% ee, respectively (Table 6.7). Further pursuing this concept, we examined reactions with (R)-TRIP and chiral thiourea catalysts **75** and **76**, which also had no effect on the enantioselectivity of the rearrangement. Addition of pyBOX ligands, which resulted in no enantioselectivity in reactions with scandium triflate, resulted in a slight increase in enantioselectivity in $MeNO_2$ (Table 6.7, **69** and **68**).

Table 6.7. Reaction with chiral organocatalysts and ligands.



Pursuing reactions with additives further, we examined the addition of other chiral and achiral amines. List and co-workers have reported successful asymmetric epoxidation reactions in the presence of amine additives.[194,195] Addition of NEt_3 shuts down the aza-Piancatelli rearrangement completely, as was expected from the difficulties encountered in developing an aza-Piancatelli rearrangement with non-aniline amines (Chapter 4). Interestingly, the addition of chiral Koga bases (**106-108**),[196] generously provided by the Zakarian group, did not completely shut down the reaction (Scheme 6.15). Unfortunately,

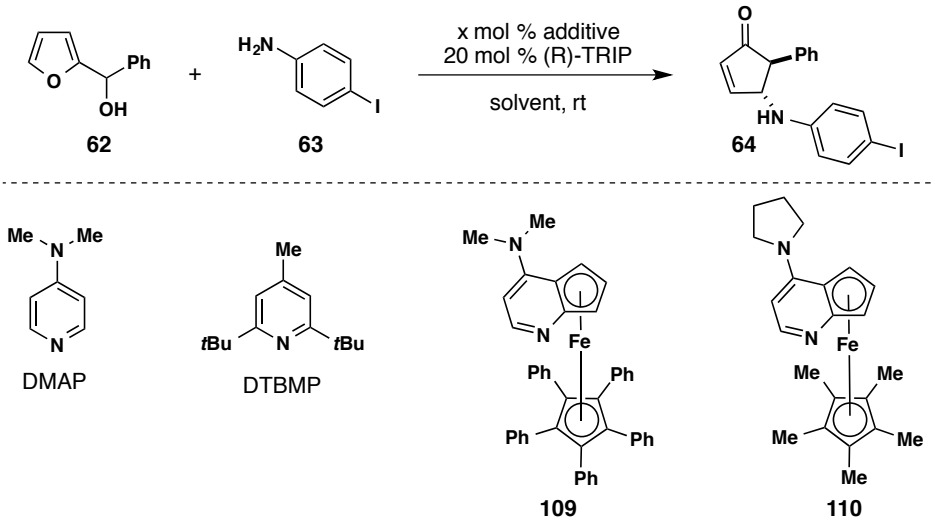
however, the products recovered from reactions in the presence of Koga bases exhibited lower enantioselectivities.



Scheme 6.15. Asymmetric aza-Piancatelli rearrangement with Koga base additives.

To our delight, addition of 4-(dimethylamino)pyridine (DMAP) or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to the reaction resulted in 49% and 50% ee, respectively (Table 6.8, entry 1 and 2). A solvent switch to $MeNO_2$ with the addition of DTBMP resulted in an unprecedented 59% ee (Table 6.8, entry 3); the highest enantioselectivity observed for an aza-Piancatelli rearrangement to date. Varying the amount of DTBMP had little effect on the enantioselectivity (Table 6.8, entry 4 and 5), but the balance between reactivity and enantioselectivity was achieved with equimolar ratios of (R)-TRIP and DTBMP (Table 6.8, entry 3). Attempting to further increase the selectivity, we tested Gregory Fu's chiral DMAP catalysts **109** and **110**,[197,198] but found that selectivities were not affected (Table 6.8, entry 6 and 7).

Table 6.8. Asymmetric aza-Piancatelli rearrangement with amine additives.



Entry	Additive	x	Solvent	% ee
1	DMAP	20	MeCN	49
2	DTBMP	20	MeCN	50
3	**DTBMP**	**20**	**$MeNO_2$**	**59**
4	DTBMP	10	$MeNO_2$	57
5[a]	DTBMP	40	$MeNO_2$	61
6	**109**	15	MeCN	40
7	**110**	15	MeCN	41

[a] Although this is the highest observed enantioselectivity, the reaction was inhibited by the presence of additional DTBMP.

Currently, the best results for the asymmetric aza-Piancatelli rearrangement are achieved when using a combination of 20 mol % (R)-TRIP and 20 mol % DTBMP in $MeNO_2$, resulting in up to 59% ee. Although there is still much room for improvement in the asymmetric aza-Piancatelli, the current progress is impressive in its own right and further studies will certainly result in the desired >90% enantiomeric excess.

6.4. Future Directions

Much work has been done in the area of the asymmetric aza-Piancatelli, but there are still paths that have been largely unexplored. Considering the amount of avenues explored with limited success certainly indicate that this reaction might benefit from MacMillan's

accelerated serendipity approach.[199] In the meantime, further investigations into other chiral phosphoric acids and derivatives could lead to greater enantioselectivity. Although the synthesis of chiral phosphoric acids is cumbersome, there clearly is a fine line between reactivity and selectivity in the aza-Piancatelli, and synthesis of the "right" catalyst could strike the necessary balance. Additionally, the current success with additives suggests that there may be a perfectly suitable additive that can generate the desired cyclopentenones in good yield and enantioselectivity. For example, the addition of chiral boronic acids, which was recently reported by Toste and co-workers,[200] may be a new avenue to explore. Reactions with other chiral metals such as chiral bismuth complexes,[201,202] derivatives of Shibasaki's REMB rare earth complexes,[203] or chiral zinc or iron complexes might also be investigated.[204,205]

Some recent forays into NaBArF (**70**) as an additive have shown that the aza-Piancatelli rearrangement proceeds at lower temperatures and, more importantly, in nonpolar solvents such as toluene. The ability to perform the aza-Piancatelli rearrangement in nonpolar solvents opens up new windows of opportunity in terms of influencing tight binding between catalyst and substrate. It may be worth pursuing the reaction in toluene with chiral phosphoric acids and NaBArF and other additives.

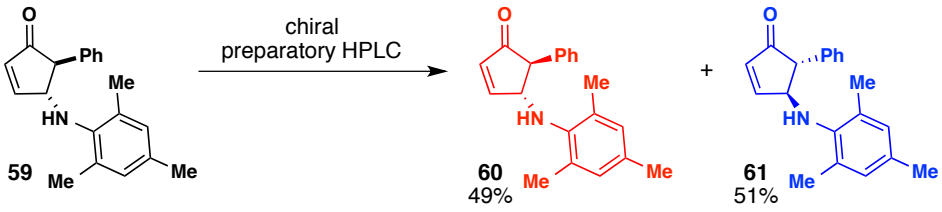
Another avenue that might be considered is the use of ionic liquids for the reaction. Dr. Donald Wenz successfully performed some aza-Piancatelli rearrangements in ionic liquids. If using a chiral ionic liquid, it is possible that the chiral medium itself could induce enantioselectivity.[206]

Finally, theoretical studies as well as kinetic and mechanistic analyses along the lines of our recent collaboration with the Hein lab might lead to insights regarding the binding mode

of the catalyst and substrate that leads to torquoselective cyclization. Such a basic understanding could guide reaction development.

6.5. Experimental Procedures

General Information. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using an Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 0.040 – 0.063 mm, Geduran). Chiral HPLC data was obtained on a Shimadzu instrument equipped with LC-6AD pumps and a diode array detector using HPLC grade hexanes and isopropyl alcohol (IPA) as eluents. The chiral columns employed were Chiralpak IA (4.6 mm diameter x 250 mmL with 5 µm particle size) and Chiralpak IB (4.6 mm diameter x 250 mmL with 5 µm particle size). HPLC spectra were examined at 254 nm wavelength. Enantiomeric excess (ee) is determined from the ratio of one enantiomer (R) to the other enantiomer (S) using the equation: ee = ((R–S)/(R+S))x100.

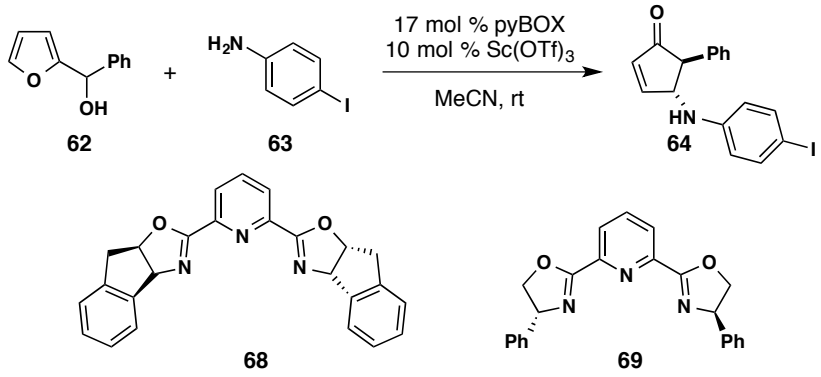


Reversibility Studies. To determine the reversibility of the rearrangement, the enantiomers of cyclopentenone **59** were separated via preparatory chiral HPLC using an OJ-H preparatory column eluting with 5% IPA in hexanes on the Zakarian group's instrument.

The purity of the single enantiomer was confirmed by analytical HPLC on a Chiralpak IA column eluting with 10% IPA in hexanes (retention times: 7.24 min, 9.16 min), before submitting it to test reactions. Reversibility studies were all performed using solutions of cyclopentenone **60** or **61** in MeCN with conditions as summarized in Table 6.1.

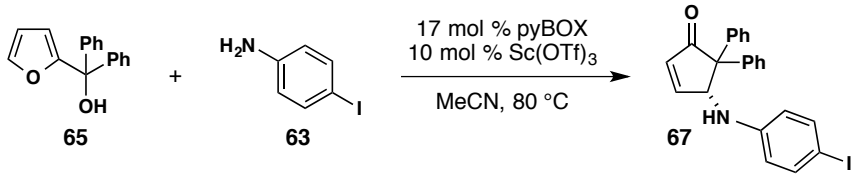
6.5.1. Reactions with Chiral Lewis Acid Complexes.

General Procedure. *Unless otherwise stated, reactions were set up as follows.* A solution of $RE(OTf)_3$ and chiral ligand in MeCN was stirred at rt for thirty minutes prior to addition of a solution of furylcarbinol **62** and *p*-iodoaniline (**63**) in MeCN. The reaction was monitored by TLC and, upon completion or after a sufficient amount of product had formed by TLC, was quenched with saturated $NaHCO_3$ and extracted (3x EtOAc). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **64.**



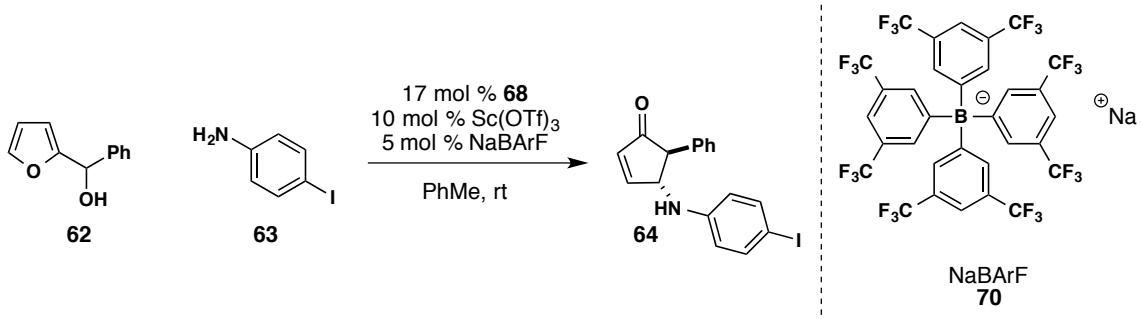
Reaction with 68:[169,170] Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.4 mg, 0.029 mmol), pyBOX **68** (1.9 mg, 0.0049 mmol), $Sc(OTf)_3$ (1.4 mg, 0.0029 mmol), 1 mL MeCN. 0% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 19.91, 29.47).

Reaction with 69:[169,170] Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.4 mg, 0.029 mmol), pyBOX **69** (1.8 mg, 0.0049 mmol), $Sc(OTf)_3$ (1.4 mg, 0.0029 mmol), 1 mL MeCN. 0% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 19.47, 28.9).

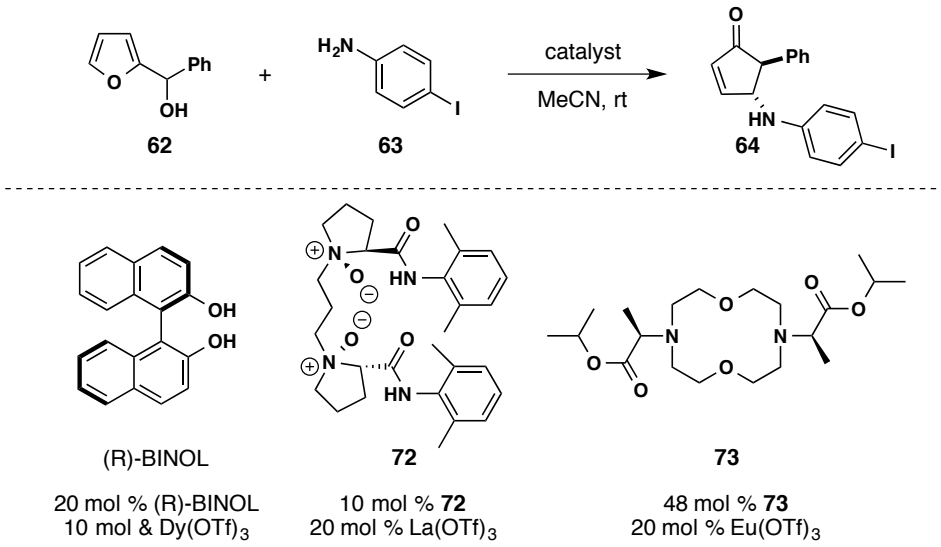


Reaction with 68:[169,170] Furylcarbinol **65** (50.1 mg, 0.20 mmol), *p*-iodoaniline (43.8 mg, 0.20 mmol), pyBOX **68** (13.4 mg, 0.034 mmol), $Sc(OTf)_3$ (9.84 mg, 0.020 mmol), 5 mL MeCN. 0% ee (Chiralpak IA, 1.0 mL/min, 10% IPA retention times: 9.27 min, 9.92 min).

Reaction with 69:[169,170] Furylcarbinol **65** (50.1 mg, 0.20 mmol), *p*-iodoaniline (43.8 mg, 0.20 mmol), pyBOX **69** (12.6 mg, 0.034 mmol), $Sc(OTf)_3$ (9.84 mg, 0.020 mmol), 5 mL MeCN. 0% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 8.93 min, 9.58 min).



Reaction with 68 and NaBArF: Furylcarbinol **62** (10.0 mg, 0.057 mmol), *p*-iodoaniline (12.6 mg, 0.20 mmol), **68** (3.8 mg, 0.0098 mmol), $Sc(OTf)_3$ (2.8 mg, 0.0057 mmol), NaBArF (**70**) (2.5 mg, 0.0029 mmol), 2 mL PhMe. 10% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.26 min *minor*, 24.73 min *major*).



Reaction with (R)-BINOL: Furylcarbinol **62** (13.1 mg, 0.075 mmol), *p*-iodoaniline (16.4 mg, 0.075 mmol), (R)-BINOL (6.6 mg, 0.026 mmol), $Dy(OTf)_3$ (9.1 mg, 0.015 mmol), 2.5 mL MeCN. 0% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.89 min, 26.22 min).

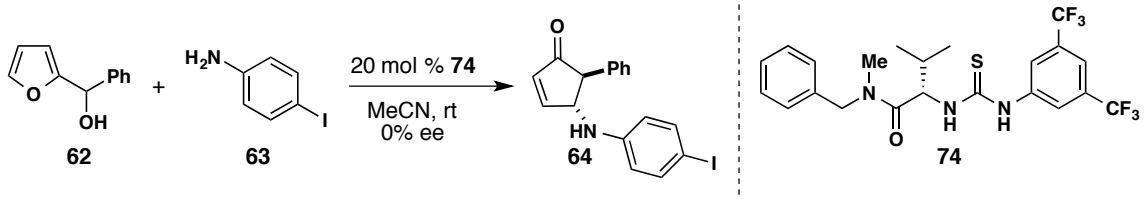
Reaction with 72:[175,176] Furylcarbinol **62** (20.0 mg, 0.11 mmol), *p*-iodoaniline (24.1 mg, 0.11 mmol), **72** (12.9 mg, 0.022 mmol), $La(OTf)_3$ (5.6 mg, 0.011 mmol), 3 mL MeCN. 0% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.83 min, 25.74 min).

Reaction with 73:[177] Furylcarbinol **62** (2.0 mg, 0.011 mmol), *p*-iodoaniline (2.5 mg, 0.011 mmol), **73** (2.2 mg, 0.0055 mmol), $Eu(OTf)_3$ (1.4 mg, 0.0023 mmol), 1 mL MeCN. 0% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.57 min, 25.81 min).

6.5.2. Reactions with Chiral Organocatalysts

General Procedure. A solution of furylcarbinol **62** and *p*-iodoaniline (**63**) in MeCN was treated with the organocatalyst and stirred at rt. The reaction was monitored by TLC and, upon completion or after a sufficient amount of product had formed by TLC, was quenched with saturated $NaHCO_3$ and extracted (3x EtOAc). The combined organic layers were dried

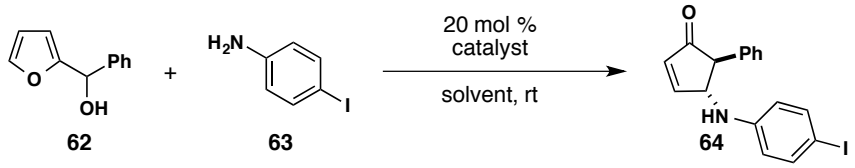
over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **64.**

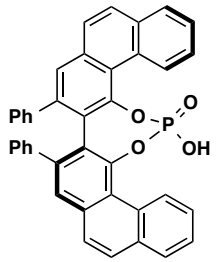


Reaction with 74: Furylcarbinol **62** (10.0 mg, 0.057 mmol), *p*-iodoaniline (13.1 mg, 0.057 mmol), **74** (6.1 mg, 0.012 mmol), 1 mL MeCN. 0% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 13.93 min, 20.07 min).

6.5.3. Reactions with Chiral Phosphoric Acids

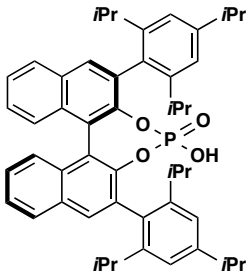
General Procedure. A solution of furylcarbinol **62** and *p*-iodoaniline (**63**) in the desired solvent was treated with the chiral phosphoric acid and stirred at rt. The reaction was monitored by TLC and, upon completion or after a sufficient amount of product had formed by TLC, was quenched with saturated $NaHCO_3$ and extracted (3x EtOAc). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **64.**





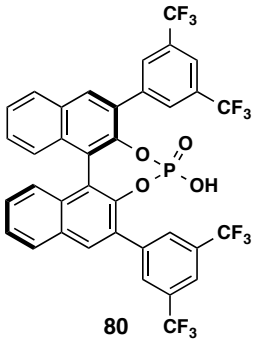
(R)-VAPOL

Reaction with (R)-VAPOL: Furylcarbinol **62** (6.3 mg, 0.036 mmol), *p*-iodoaniline (7.9 mg, 0.036 mmol), (R)-VAPOL (4.0 mg, 0.0067 mmol), 1 mL MeCN. 0% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.58 min, 25.88 min).



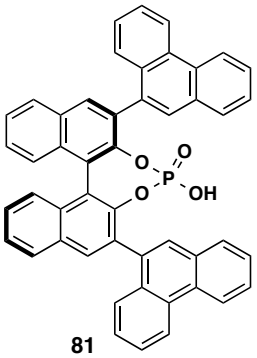
(R)-TRIP

Reaction with (R)-TRIP: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), 0.5 mL solvent. MeCN: 46% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.40 min *minor*, 25.28 min *major*). $MeNO_2$: 49% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 13.85 min *minor*, 19.99 min *major*). PhMe: 29% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 13.66 min *minor*, 19.62 min *major*). CH_2Cl_2: 19 % ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 14.20 min *minor*, 20.44 min *major*).



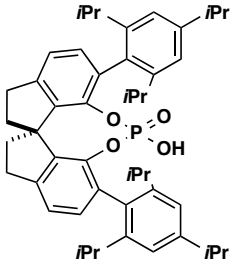
80

Reaction with 80: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.4 mg, 0.029 mmol), **80** (4.5 mg, 0.0058 mmol), 1 mL solvent. MeCN: 5% ee (Chiralpak IA, retention times: 14.13 min *minor*, 20.50 min *major*). PhMe: 34% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.71 min *minor*, 25.88 min *major*).



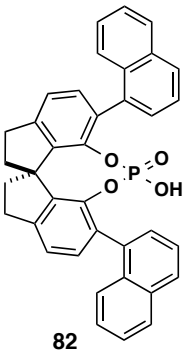
81

Reaction with 81: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.4 mg, 0.029 mmol), **81** (4.1 mg, 0.0058 mmol), 1 mL solvent. MeCN: 9% ee (Chiralpak IB, retention times: 19.77 min *minor*, 25.96 min *major*). PhMe: 12% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.53 min *minor*, 25.76 min *major*).



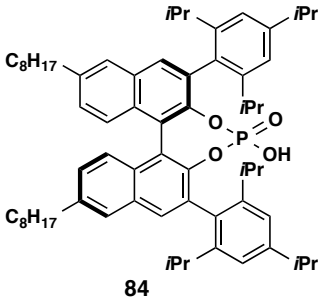
(R)-STRIP

Reaction with (R)-STRIP: Furylcarbinol **62** (2.0 mg, 0.011 mmol), *p*-iodoaniline (2.4 mg, 0.011 mmol), (R)-STRIP (1.6 mg, 0.0022 mmol), 0.5 mL MeCN. 12% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.84 min *minor*, 25.73 min *major*).



82

Reaction with 82: Furylcarbinol **62** (2.0 mg, 0.011 mmol), *p*-iodoaniline (2.4 mg, 0.011 mmol), **82** (1.2 mg, 0.0022 mmol), 0.5 mL MeCN. 5% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.56 min *minor*, 25.48 min *major*).

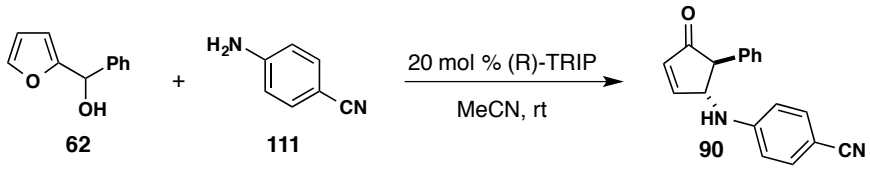


84

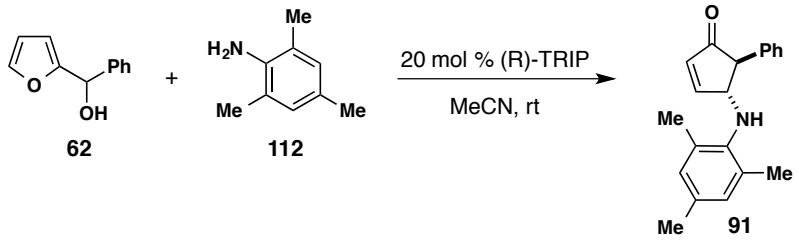
Reaction with 84: Furylcarbinol **62** (2.0 mg, 0.011 mmol), *p*-iodoaniline (2.4 mg, 0.011 mmol), **84** (2.2 mg, 0.0022 mmol), 0.5 mL MeCN. 36% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.16 min *minor*, 23.97 min *major*).

6.5.4. Reaction Scope with (R)-TRIP

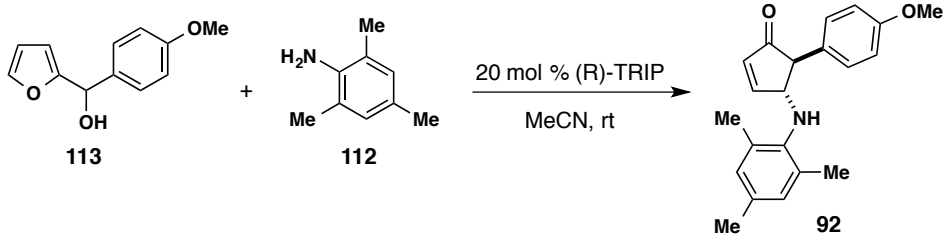
General Procedure. A solution of furylcarbinol and aniline in the desired solvent was treated with (R)-TRIP and stirred at rt. The reaction was monitored by TLC and, upon completion or after a sufficient amount of product had formed by TLC, was quenched with saturated $NaHCO_3$ and extracted (3x EtOAc). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone**.**



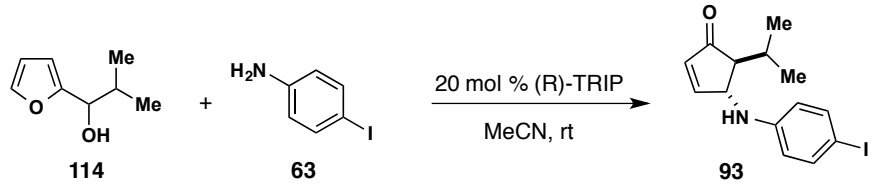
90: Furylcarbinol **62** (2.6 mg, 0.015 mmol), 4-aminobenzonitrile (**111**) (1.8 mg, 0.015 mmol), (R)-TRIP (2.3 mg, 0.0030 mmol) in 1 mL MeCN. 43% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 43.84 min *minor*, 56.05 min *major*).



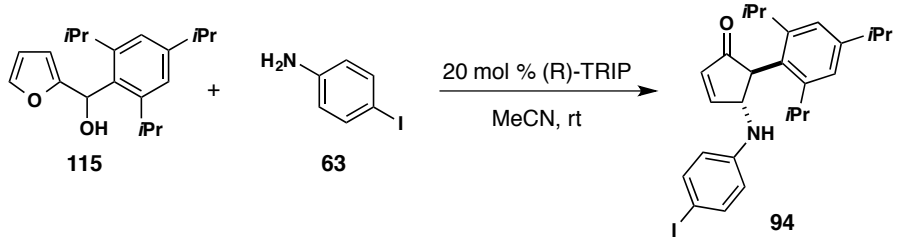
91: Furylcarbinol **62** (5.0 mg, 0.029 mmol), 2,4,6-trimethylaniline (**112**) (3.9 mg, 0.029 mmol), (R)-TRIP (4.4 mg, 0.0058 mmol) in 1 mL MeCN. 52% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 7.07 min *minor*, 8.93 min *major*).



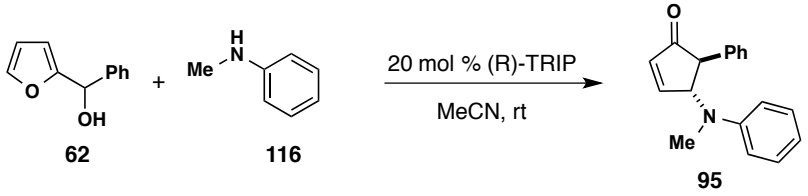
92: Furylcarbinol **113** (2.9 mg, 0.014 mmol), 2,4,6-trimethylaniline (**112**) (1.9 mg, 0.014 mmol), (R)-TRIP (2.1 mg, 0.0028 mmol) in 0.5 mL MeCN. 47% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 10.16 min *minor*, 13.12 min *major*).



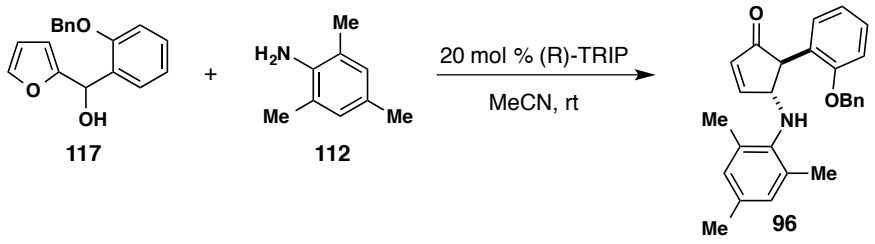
93: Furylcarbinol **114** (4.2 mg, 0.030 mmol), *p*-iodoaniline (6.4 mg, 0.030 mmol), (R)-TRIP (4.5 mg, 0.006 mmol) in 0.5 mL MeCN. 27% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 7.68 min *minor*, 9.17 min *major*).



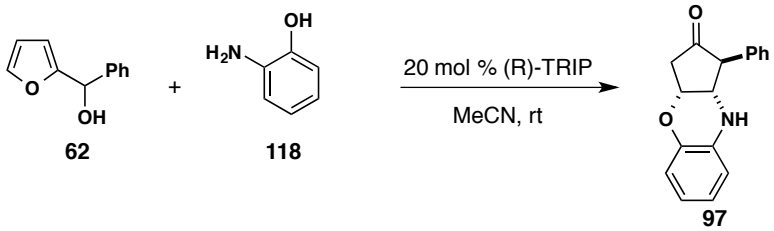
94: Furylcarbinol **115** (4.2 mg, 0.014 mmol), *p*-iodoaniline (3.1 mg, 0.014 mmol), (R)-TRIP (2.1 mg, 0.0028 mmol) in 0.5 mL MeCN. 16% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 6.88 min *minor*, 8.26 min *major*).



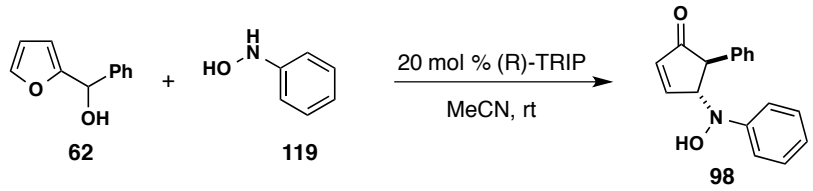
95: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *N*-methylaniline (**116**) (3.1 mg, 0.029 mmol), (R)-TRIP (4.4 mg, 0.0058 mmol) in 1 mL MeCN. 4% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 10.17 min *minor*, 11.20 min *major*).



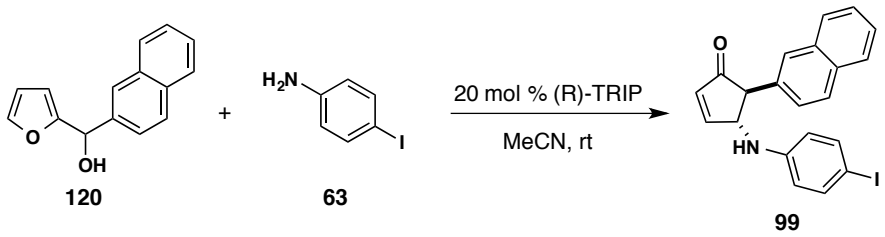
96: Furylcarbinol **117** (5.0 mg, 0.018 mmol), 2,4,6-trimethylaniline (**112**) (2.4 mg, 0.018 mmol), (R)-TRIP (2.7 mg, 0.0036 mmol) in 1 mL MeCN. 49% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 10.15 min *major*, 11.07 min *minor*).



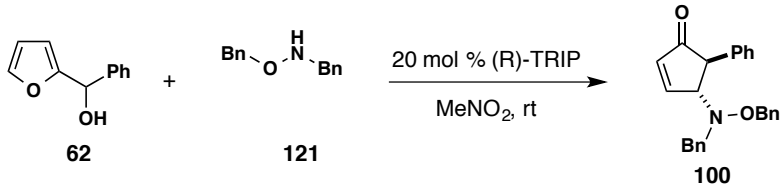
97: Furylcarbinol **62** (5.0 mg, 0.029 mmol), 2-aminophenol (**118**) (3.2 mg, 0.029 mmol), (R)-TRIP (4.4 mg, 0.0058 mmol) in 1 mL MeCN. 7% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.12 min *minor*, 24.44 min *major*).



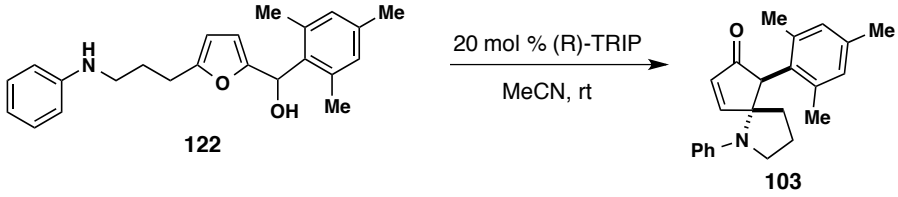
98: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *N*-phenylhydroxlamine (**119**) (1.6 mg, 0.015 mmol), (R)-TRIP (2.5 mg, 0.0030 mmol) in 0.5 mL MeCN. 41% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 12.62 min *minor*, 12.74 min *major*).



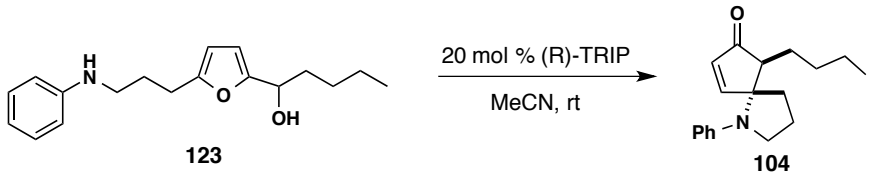
99: Furylcarbinol **120** (3.3 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.3 mg, 0.0030 mmol) in 0.5 mL MeCN. 41% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 26.33 min *minor*, 38.12 min *major*).



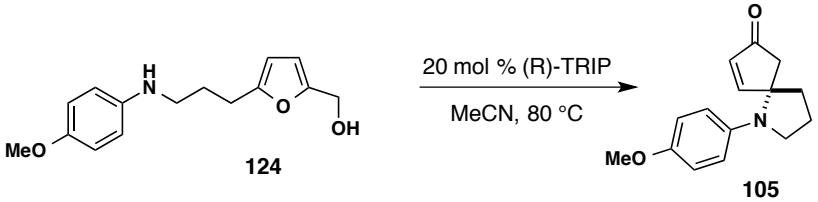
100: Furylcarbinol **62** (2.0 mg, 0.012 mmol), *N,O*-dibenzylhydroxylamine (**121**) (2.5 mg, 0.012 mmol), (R)-TRIP (1.7 mg, 0.0023 mmol) in 0.5 mL $MeNO_2$. 42% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 7.38 min, 9.82 min).



103: Furylcarbinol **122** (2.3 mg, 0.0066 mmol), (R)-TRIP (1.0 mg, 0.0013 mmol) in 0.5 mL MeCN. 36% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 5.94 min *minor*, 67.93 min *major*).

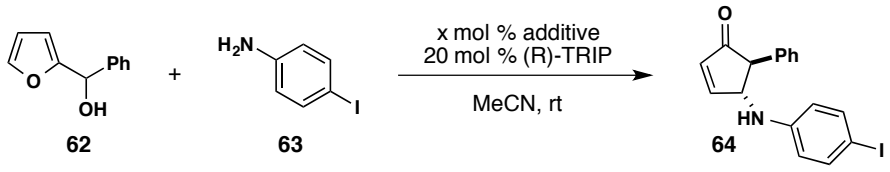


104: Furylcarbinol **123** (5.0 mg, 0.017 mmol), (R)-TRIP (2.6 mg, 0.0034 mmol) in 0.5 mL MeCN. 32% ee (Chiralpak IA, 1.0 mL/min, 10% IPA; retention times: 4.90 min *minor*, 5.35 min *major*).



105: Furylcarbinol **124** (2.0 mg, 0.077 mmol), (R)-TRIP (1.1 mg, 0.0015 mmol) in 0.5 mL MeCN at 80 °C. 8% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 9.71 min, 10.79 min).

6.5.5. Reaction Scope with (R)-TRIP and Additives



General Procedure. A solution of furylcarbinol **62** and aniline **63** in the desired solvent was treated with the additive and (R)-TRIP and stirred at rt. The reaction was monitored by TLC and, upon completion or after a sufficient amount of product had formed by TLC, was quenched with saturated $NaHCO_3$ and extracted (3x EtOAc). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford cyclopentenone **64.**

$Dy(OTf)_3$ additive: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.4 mg, 0.029 mmol), (R)-TRIP (4.4 mg, 0.0058 mmol), $Dy(OTf)_3$ (1.8 mg, 0.0029 mmol) in 0.5 mL MeCN. 28% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.31 min *minor*, 28.52 min *major*).

MgF_2 additive:[189] Furylcarbinol **62** (2.5 mg, 0.014 mmol), *p*-iodoaniline (3.1 mg, 0.014 mmol), (R)-TRIP (2.1 mg, 0.0028 mmol), MgF_2 (0.2 mg, 0.003 mmol) in 1 mL MeCN. 44% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 21.02 min *minor*, 27.65 min *major*).

$CuCl_2$ additive:[190] Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), $CuCl_2$ (0.4 mg, 0.0030 mmol) in 0.5 mL MeCN.

39% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.35 min *minor*, 25.15 min *major*).

$Cu(OTf)_2$ additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), $Cu(OTf)_2$ (1.1 mg, 0.0030 mmol) in 0.5 mL MeCN. 27% ee (Chiralpak IB, 1.0 mL/min, 3% IPA; retention times: 44.09 min *minor*, 57.20 min *major*).

$(Ph_3P)AuCl$ additive:[191,192] Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), $(Ph_3P)AuCl$ (1.5 mg, 0.0030 mmol) in 0.5 mL PhMe. 16% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.71 min *minor*, 25.83 min *major*).

$ZnBr_2$ additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), $ZnBr_2$ (0.7 mg, 0.0030 mmol) in 0.5 mL MeCN. 27% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.51 min *minor*, 25.54 min *major*).

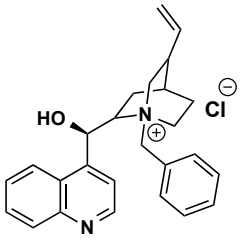
$NaHCO_3$ additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), $NaHCO_3$ (1.6 mg, 0.015 mmol) in 0.5 mL MeCN. 5% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.78 min *minor*, 25.98 min *major*).

Basic alumina additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), basic alumina (small scoop, ~10 mg, 0.1 mmol) in 0.5 mL MeCN. 44% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 20.48 min *minor*, 27.09 min *major*).

AcOH additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), AcOH (0.14 mg, 0.0023 mmol) in 0.5 mL MeCN.

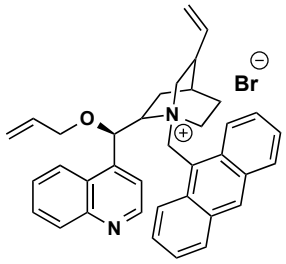
45% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.76 min *minor*, 25.98 min *major*).

HFIP additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), HFIP (0.3 μL, 0.0030 mmol) in 0.5 mL MeCN. 47% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.93 min *minor*, 26.16 min *major*).



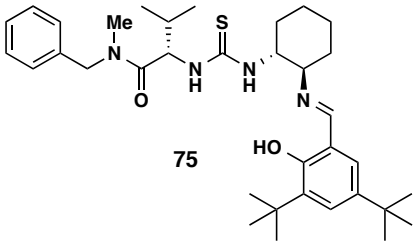
79

79 additive:[193] Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.6 mg, 0.029 mmol), (R)-TRIP (4.5 mg, 0.0060 mmol), **79** (2.5 mg, 0.0060 mmol) in 1 mL MeCN. 34% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.94 min *minor*, 26.38 min *major*).



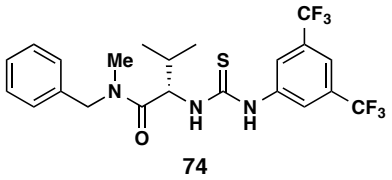
78

79 additive: [193] Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.6 mg, 0.029 mmol), (R)-TRIP (4.5 mg, 0.0060 mmol), **79** (3.6 mg, 0.0060 mmol) in 1 mL MeCN. 44% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.83 min *minor*, 26.16 min *major*).



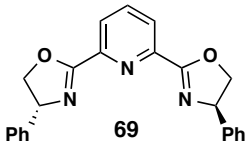
75

75 additive: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.6 mg, 0.029 mmol), (R)-TRIP (4.5 mg, 0.0060 mmol), **75** (3.6 mg, 0.0060 mmol) in 1 mL MeCN. 42% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.85 min *minor*, 26.11 min *major*).



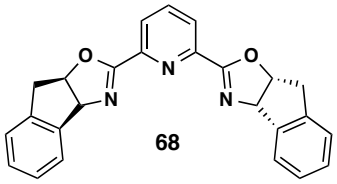
74

74 additive: Furylcarbinol **62** (5.0 mg, 0.029 mmol), *p*-iodoaniline (6.6 mg, 0.029 mmol), (R)-TRIP (4.5 mg, 0.0060 mmol), **74** (3.0 mg, 0.0060 mmol) in 1 mL MeCN. 45% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.54 min *minor*, 25.63 min *major*).



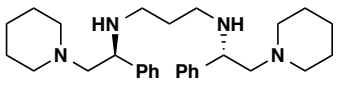
69

69 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **69** (1.1 mg, 0.0030 mmol) in 0.5 mL $MeNO_2$. 53% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.66 min *minor*, 25.49 min *major*).



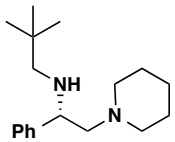
68

68 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **68** (1.2 mg, 0.0030 mmol) in 0.5 mL $MeNO_2$. 51% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.66 min *minor*, 25.65 min *major*).



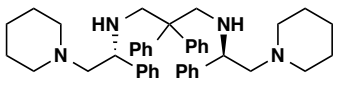
106

106 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **106** (1.3 mg, 0.0030 mmol) in 0.5 mL MeCN. 6% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.65 min *minor*, 25.71 min *major*).



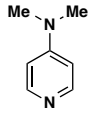
107

107 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **107** (0.8 mg, 0.0030 mmol) in 0.5 mL MeCN. 7% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.72 min *minor*, 25.88 min *major*).



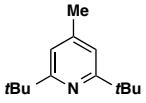
108

108 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **108** (1.8 mg, 0.0030 mmol) in 0.5 mL MeCN. 17% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.90 min *minor*, 26.14 min *major*).



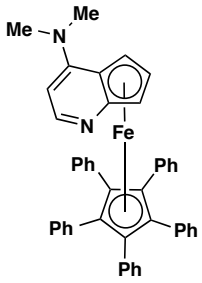
DMAP

DMAP additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), DMAP (0.3 mg, 0.0030 mmol) in 0.5 mL MeCN. 49% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 20.47 min *minor*, 26.90 min *major*).



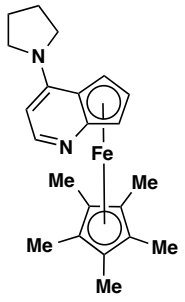
DTBMP

DTBMP additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.3 mg, 0.0030 mmol), DTBMP (0.5 mg, 0.0030 mmol) in 0.5 mL solvent. MeCN: 50% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 20.17 min *minor*, 26.59 min *major*). $MeNO_2$: 59% ee ((Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.63 min *minor*, 25.63 min *major*).



109

109 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **109** (1.5 mg, 0.0030 mmol) in 0.5 mL MeCN. 40% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.82 min *minor*, 26.04 min *major*).



110

110 additive: Furylcarbinol **62** (2.6 mg, 0.015 mmol), *p*-iodoaniline (3.3 mg, 0.015 mmol), (R)-TRIP (2.2 mg, 0.0030 mmol), **110** (0.8 mg, 0.0030 mmol) in 0.5 mL MeCN. 41% ee (Chiralpak IB, 1.0 mL/min, 10% IPA; retention times: 19.74 min *minor*, 25.91 min *major*).

6.5.6. Select HPLC Traces

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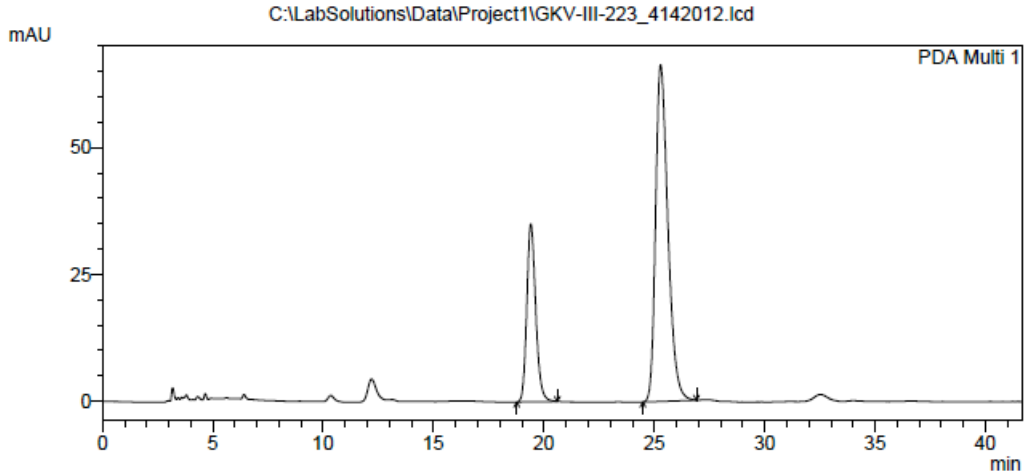

1 PDA Multi 1/254nm 4nm

<Results>

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PDA Ch1 254nm 4nm

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2	25.284	2578332	72.330
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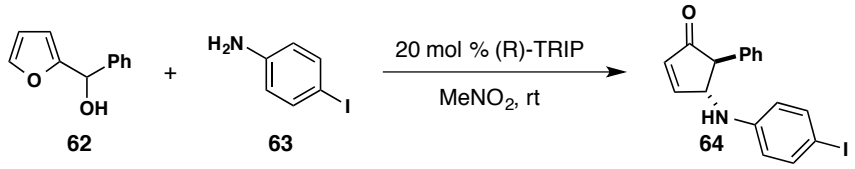

62 63 64

Acquired by	: Admin
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Sample ID	: GKV-II-079-2_run1
Vail #	: 17
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Method File Name	: dtest.lcm
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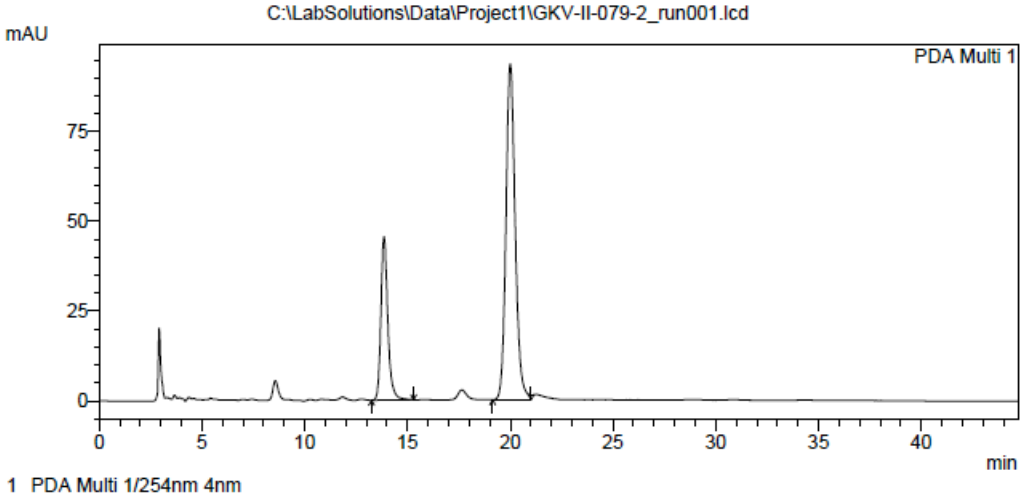

1 PDA Multi 1/254nm 4nm

<Results>

PeakTable

PDA Ch1 254nm 4nm

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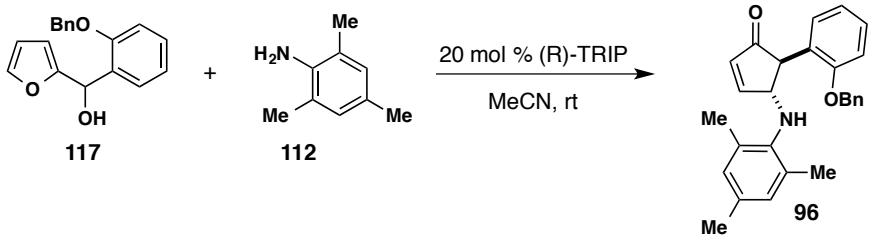

Acquired by	: Admin
Sample Name	: GKV-II-162-2_63011
Sample ID	: GKV-II-162-2_63011
Vail #	: 3
Injection Volume	: 100 uL
Data File Name	: GKV-II-162-2_63011.lcd
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Batch File Name	:
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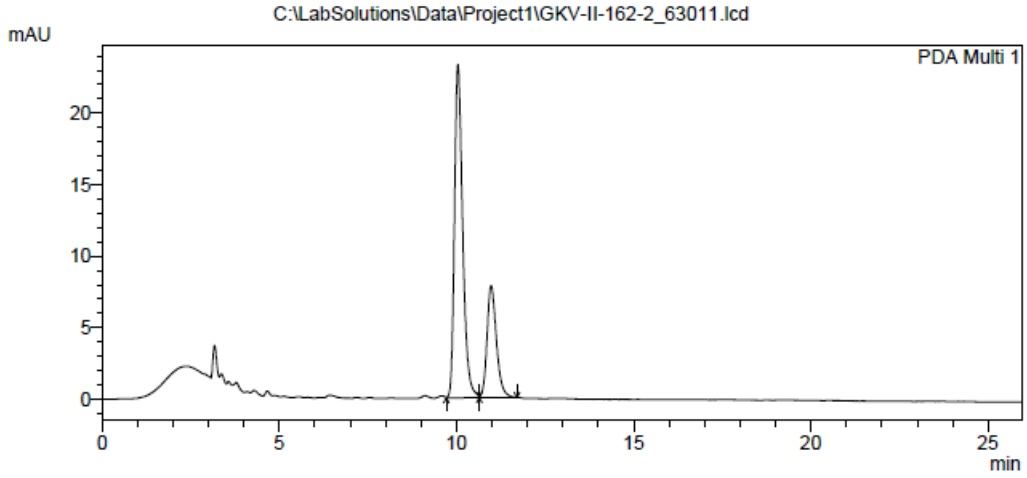

1 PDA Multi 1/254nm 4nm

<Results>

PeakTable

PDA Ch1 254nm 4nm

Peak#	Ret. Time	Area	Area %
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2	10.976	144820	27.925
Total		518604	100.000

7. The (Aza-)Piancatelli Rearrangement in Total Synthesis

7.1. Natural Products Accessible via an (Aza-)Piancatelli Rearrangement

The Piancatelli and aza-Piancatelli rearrangements are exceptional methods for expedient synthesis of densely functionalized cyclopentenones from cheap, sustainable starting materials. Piancatelli originally investigated the transformation of furylcarbinols because of an interest in the synthesis of prostaglandins.[39] The rearrangement has since been successfully applied to the synthesis of prostaglandin E1 (Figure 7.1, **1**),[54] as well as a number of other approaches to natural products.[207–209] Coralloidolide F[210] (**2**) and jogyamycin (**3**)[211] are two natural products whose synthesis has not been accomplished that could also be accesses via a Piancatelli rearrangement. Due to the novelty of the aza-Piancatelli rearrangement, its potential in terms of natural product synthesis has not yet been realized. In our first communication detailing the aza-Piancatelli rearrangement we demonstrated the value of the reaction with the synthesis of an hNK1 inhibitor (**4**).[78] Following the development of an intramolecular aza-Piancatelli rearrangement to access azaspirocycles,[138] we have had a continued interest in the synthesis of homoharringtonine[212] and stemonamine.[213]

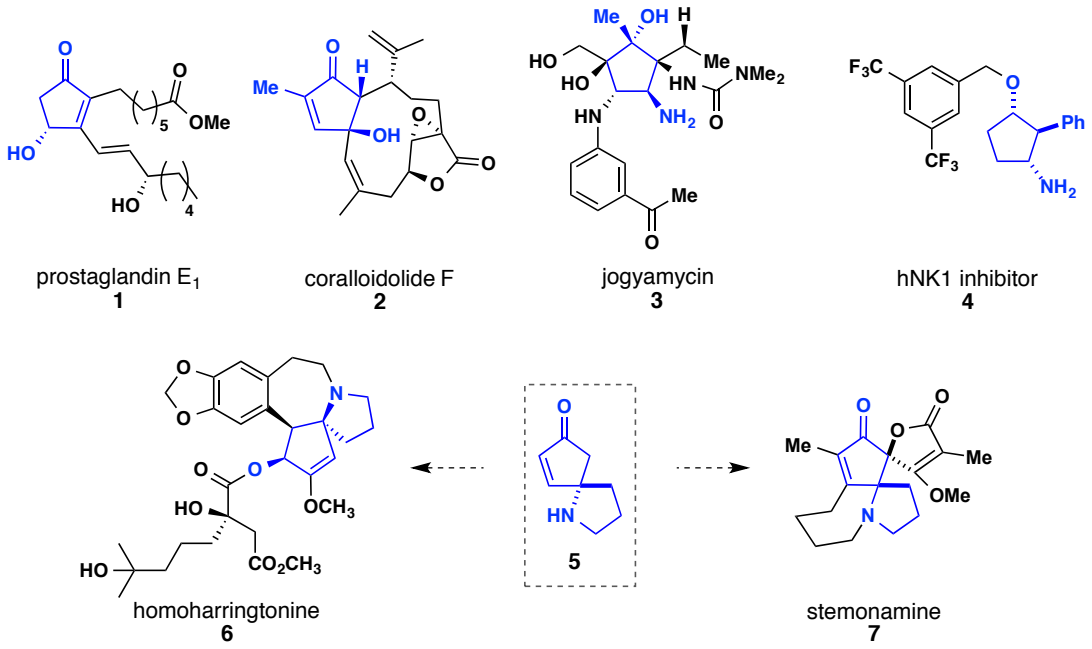


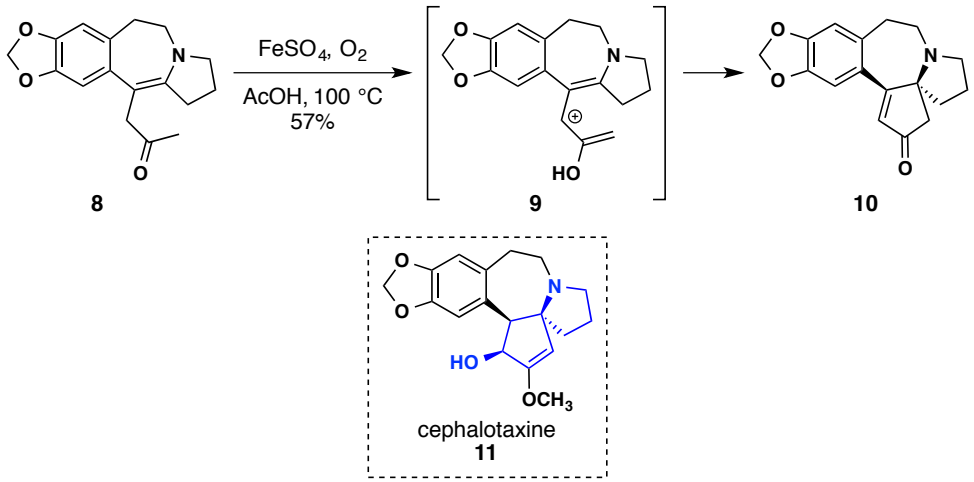
Figure 7.1. Natural products containing the substituted cyclopentenone motif.

7.2. Efforts Toward the Total Synthesis of Cephalotaxine and Homoharringtonine

Early on in the development of an intramolecular aza-Piancatelli rearrangement, we recognized the potential of this rearrangement in terms of its application to the total synthesis of homoharringtonine. The presence of the azaspirocyclic cyclopentenone makes it an ideal target for the intramolecular aza-Piancatelli rearrangement.

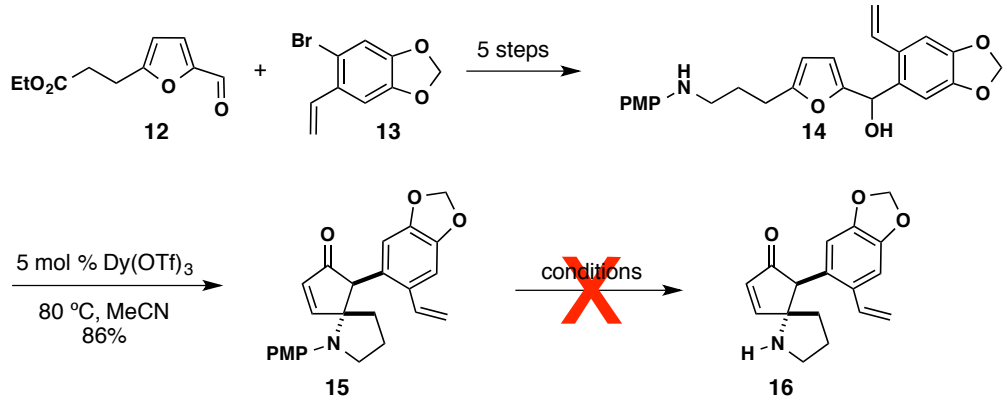
Homoharringtonine is a plant alkaloid member of the cephalotaxus group of natural products isolated from coniferous *Cephalotaxus* evergreen trees found in China.[214] Many studies have shown homoharringtonine to have exceptional antitumor properties and in 2012 it was approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic myeloid leukemia (CML) with resistance to treatment with tyrosine kinase inhibitors.[215] Homoharringtonine differs from the parent alkaloid cephalotaxine (**11**) only by the presence of an ester side chain. Although cephalotaxine possesses no relevant biological activity, many synthetic efforts have focused on its synthesis,[216–221] since subsequent esterification is

a known process.[212,222] Interestingly, several syntheses make use of a Nazarov cyclization to generate the cyclopentene unit (Scheme 7.1).[223,224]



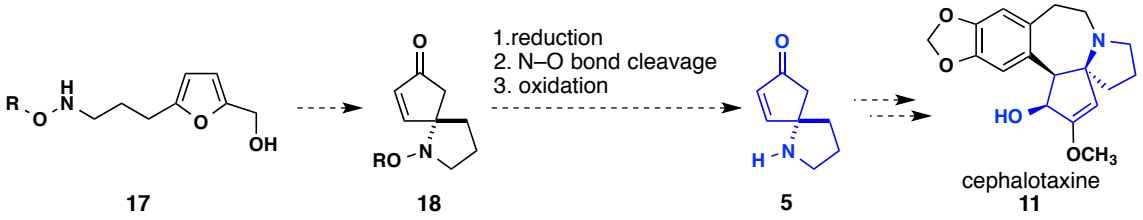
Scheme 7.1. Approach to cephalotaxine via a Nazarov-type reaction.

Our efforts have been focused on synthesizing the core of cephalotaxine via an aza-Piancatelli rearrangement. The first approach to cephalotaxine by our group was based on the intramolecular aza-Piancatelli rearrangement with tethered aniline nucleophiles.[225] The precursor furylcarbinol (**14**) was synthesized in just five steps from **12** and **13**, and readily underwent the dysprosium catalyzed rearrangement affording cyclopentenone **15** in 86% yield (Scheme 7.2). To our disappointment and despite previous success with removing the PMP group to access the hNK1 inhibitor (Chapter 2, Scheme 2.11), all efforts to access the free amine were unsuccessful, resulting in decomposition of the azaspirocycle. It became clear that we had to re-evaluate our approach to the cephalotaxine core.



Scheme 7.2. First approach to the total synthesis of cephalotaxine.

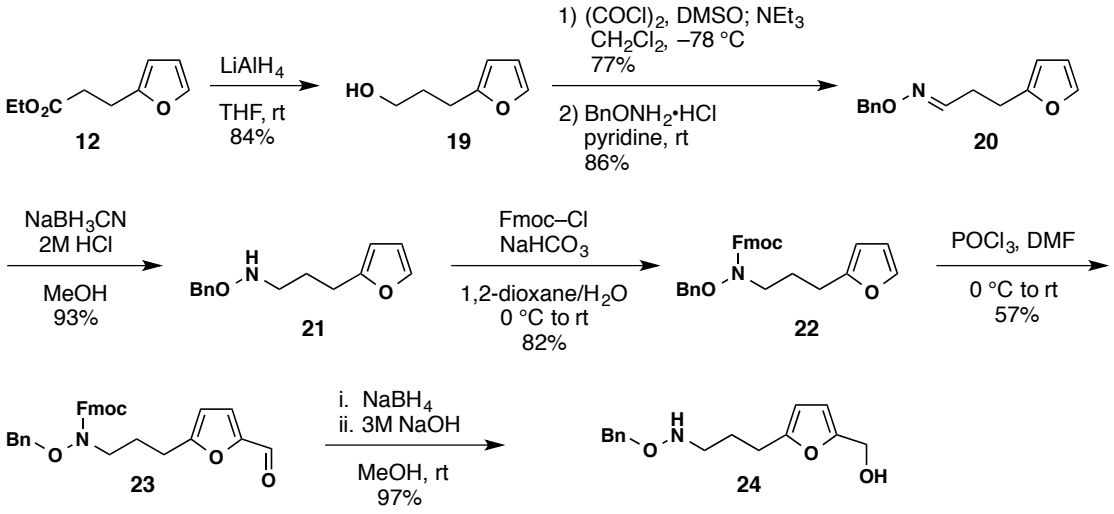
Following the development of the hydroxylamine aza-Piancatelli rearrangement, we devised a new approach to cephalotaxine that involves an intramolecular hydroxylamine aza-Piancatelli rearrangement (Scheme 7.3). Access to the free amine (**5**) would rely on our previously described three-step reduction-cleavage-oxidation protocol (Chapter 4). Subsequent functionalization steps would result in the synthesis of cephalotaxine (**11**).



Scheme 7.3. Second generation approach to cephalotaxine.

The synthesis of furylcarbinol **24** was accomplished in seven steps as depicted in Scheme 7.4. Starting from commercially available ester **12**, alcohol **19** was prepared. Subsequent Swern oxidation to the volatile, unstable aldehyde was immediately followed by condensation with *O*-benzylhydroxylamine hydrochloride to form imine **20**. Reduction with $NaBH_3CN$ gave **21** in 93% yield. Initially amine **21** was protected with di-*tert*-butyl dicarbonate (Boc), but we later discovered that removal of the protecting group was difficult. Instead, we settled on using fluorenylmethyloxycarbonyl chloride (Fmoc-Cl), and

subsequently were able to synthesize aldehyde **23** via Vilsmeier-Haack formylation. One-pot aldehyde reduction and Fmoc-deprotection with $NaBH_4$ and 3M NaOH, respectively, resulted in the desired unsubstituted furylcarbinol **24**. Using this route, we were able to access gram quantities of Fmoc-protected aldehyde **23**.

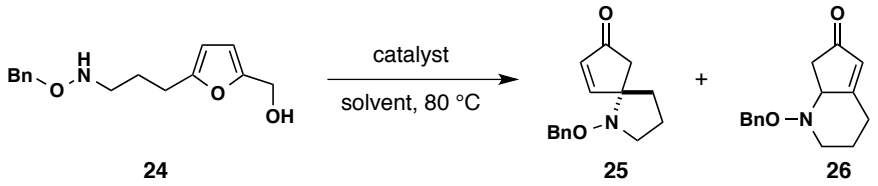


Scheme 7.4. Synthesis of unsubstituted furylcarbinol **24**.

At this stage, we were ready to test our key hydroxylamine aza-Piancatelli rearrangement. Exposing the furylcarbinol **24** to $Dy(OTf)_3$ in MeCN or $MeNO_2$ resulted in complete decomposition of the starting material (Table 7.1, entry 1 and 2). From our previous studies, we knew that primary furylcarbinols do not participate in the intermolecular aza-Piancatelli rearrangement. In the intramolecular aza-Piancatelli rearrangement, primary furylcarbinols will rearrange, but the reaction is not as robust as those with substituted secondary furylcarbinols.[138] In our experience, although less sustainable, zinc facilitated reactions tend to be milder than dysprosium catalyzed reactions, leading us to examine this finicky rearrangement with zinc bromide. To our delight, furylcarbinol **24** rearranged to the desired cyclopentenone **25** in 26% yield when treated with $ZnBr_2$ in MeCN (Table 7.1, entry 3). However, we also observed the formation of **26**,

presumably resulting from a subsequent molecular rearrangement. A simple solvent switch to $MeNO_2$, which we had already identified as a superior solvent for reactions with hydroxylamines, resulted in formation of cyclopentenone **25** in 39% yield without the formation of the side product (Table 7.1, entry 4). Knowing that the desired cyclopentenone can be formed and is isolable, we then examined a few more dysprosium catalyzed reactions. Similar to entry 1, the reaction of furylcarbinol **24** with $Dy(OTf)_3$ in toluene with addition of NaBArF resulted in decomposition (Table 7.1, entry 6). Pleasingly, using anhydrous $Dy(OTf)_3$ (dried for 48 hours under vacuum at 200 °C)[102] under highly dilute conditions resulted in formation of **25** in an excellent 56% yield.

Table 7.1. Developing reaction conditions for the rearrangement of unsubstituted furylcarbinol **24**.



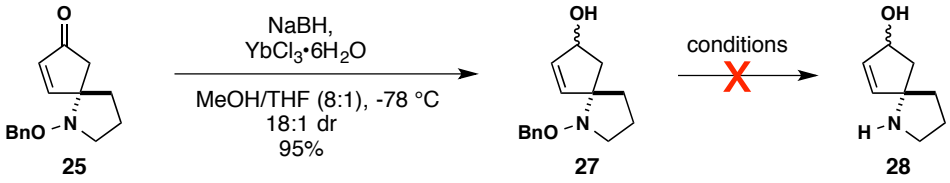
24 **25** **26**

Entry	Catalyst (mol %)	Solvent	Yield 25 (%)	Yield 26 (%)
1[a]	$Dy(OTf)_3$ (5)	MeCN	--	--
2	$Dy(OTf)_3$ (5)	$MeNO_2$	--	--
3	$ZnBr_2$ (100)	MeCN	26	14
4	**$ZnBr_2$ (100)**	**$MeNO_2$**	**39**	**--**
5[b]	$ZnBr_2$ (100)	MeCN	39	--
6[c]	$Dy(OTf)_3$ (10)	PhMe	--	--
7	**anhyd. $Dy(OTf)_3$**	**MeCN**	**56**	**--**

[a] The reaction resulted in complete decomposition of the starting material. [b] The reaction was performed with acylated **24**.[226] [c] The reaction was performed with addition of 10 mol % NaBArF at rt.

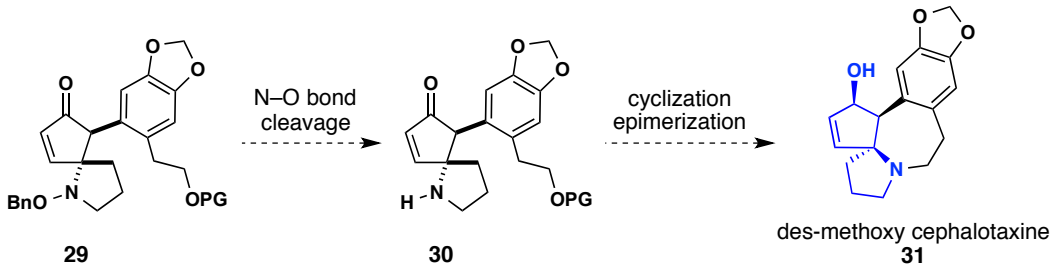
With our key cyclopentenone in hand, we were ready to examine N–O bond clipping reactions to access the free amine required to complete the synthesis of cephalotaxine. Again, cleaving the N–O bond proved to be a challenge. Use of Zn/HCl,[147] SmI_2[144] or

hydrogenation over Pd/C[145] did not result in the formation of the desired free amine (**5**). Reduction of the cyclopentenone to the allylic alcohol (**27**) proceeded nicely in 18:1 dr (Scheme 7.5). To our disappointment, our previously successful Zn/HCl protocol for cleaving the N–O bond of allylic alcohols did not work for the synthesis of the requisite free amine.



Scheme 7.5. Reduction to the allylic alcohol, and unsuccessful attempts at N–O bond cleavage.

Taking the challenges we have encountered with unsubstituted cyclopentenone **25** into consideration, we are currently investigating installation of the requisite aryl group prior to the aza-Piancatelli rearrangement, similar to the approach described in our first efforts to synthesize cephalotaxine (Scheme 7.2). Access to **29** would be followed by N–O bond cleavage to give **30**. Preliminary calculations at the B3LYP 6-31G* level of density functional theory suggest that there is only a small difference in strain between the *trans* and *cis* substituted cyclopentenones. This leads us to believe that *N*-alkylation to form the seven-membered macrocycle from the *trans*-substituted cyclopentenone should be possible. Following formation of the macrocycle, epimerization to the *cis*-substituted cyclopentenone and reduction of the ketone would furnish des-methoxy cephalotaxine (**31**) (Scheme 7.6).

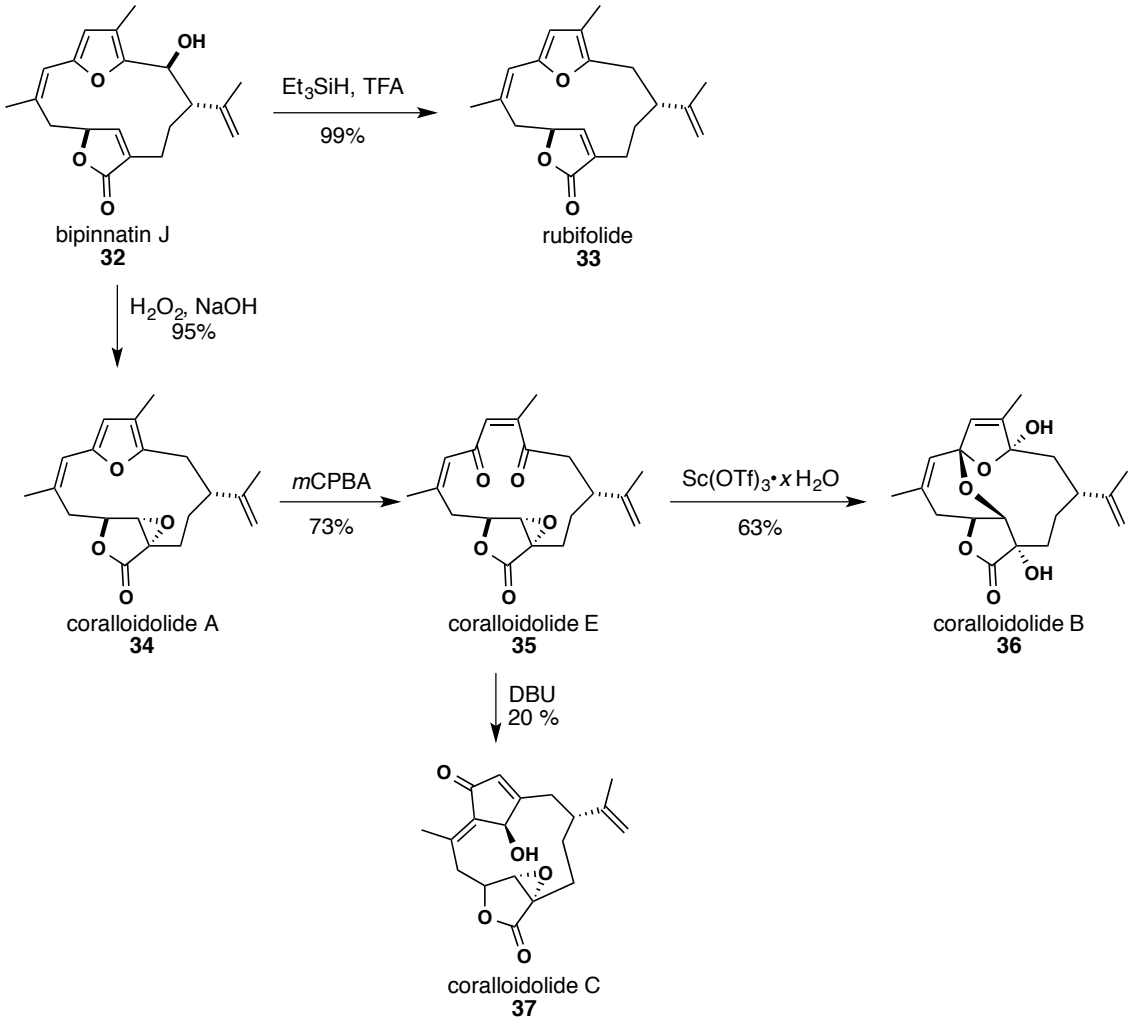


Scheme 7.6. Proposed alternative pathway to des-methoxy cephalotaxine.

Although the synthesis of cephalotaxine is not yet complete, we are confident that our toolbox of synthetic transformations and knowledge of the behavior of cyclopentenones will allow us to synthesize the natural product using our strategy. The total synthesis of cephalotaxine would certainly highlight the value of the intramolecular aza-Piancatelli rearrangement as a means for building azaspirocycles. One of the most valuable lessons learned from the synthesis thus far is that the specific substitution patterns and oxidation states of cyclopentenones, in particular those with amine substituents, greatly influence the stability of these compounds to subsequent transformations.

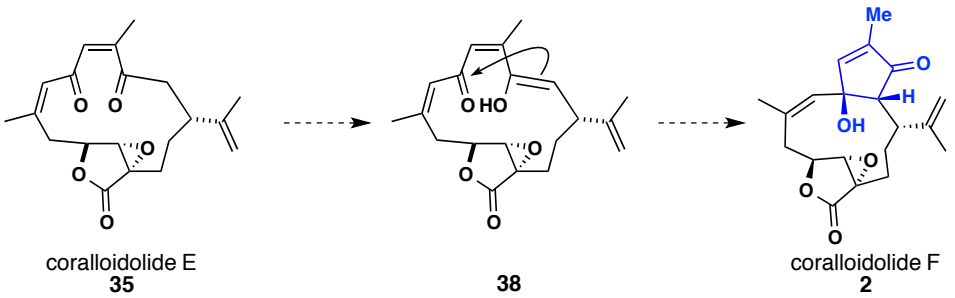
7.3. Efforts Toward the Total Synthesis of Coralloidolide F

We became interested in the total synthesis of coralloidolide F following a report by Trauner and co-workers on the total synthesis of coralloidolides A, B, C and E (Scheme 7.7).[227] The coralloidolides belong to the furanocembranoid family of natural products that has received much interest from the synthetic community.[228–231] Coralloidolides A-F are proposed to be naturally derived from rubifolide (**33**), which the Trauner group had previously accessed from bipinnatin J (**32**) (Scheme 7.7),[232] through a series of oxidations and rearrangements.



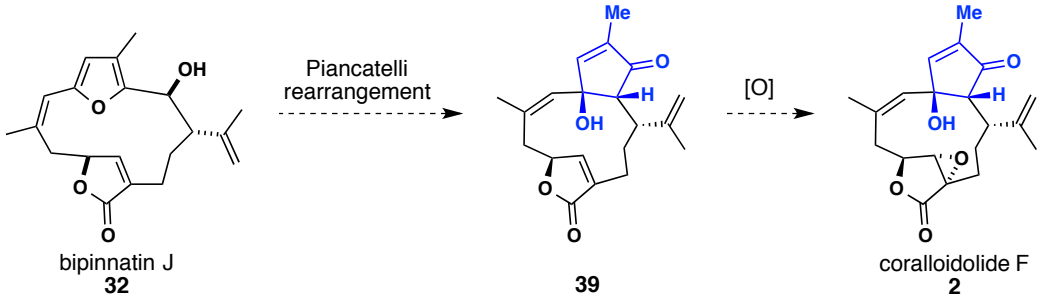
Scheme 7.7. Synthesis of rubifolide and coralloidolide A,B,C and E from bipinnatin J.

It was proposed that coralloidolide E (**35**) is the precursor to coralloidolide F (**2**), which could be accessed from a transannular aldol addition of enolate **38** (Scheme 7.8). Despite great efforts, the Trauner group was unable to access coralloidolide F via their proposed pathway, and had to accept defeat.



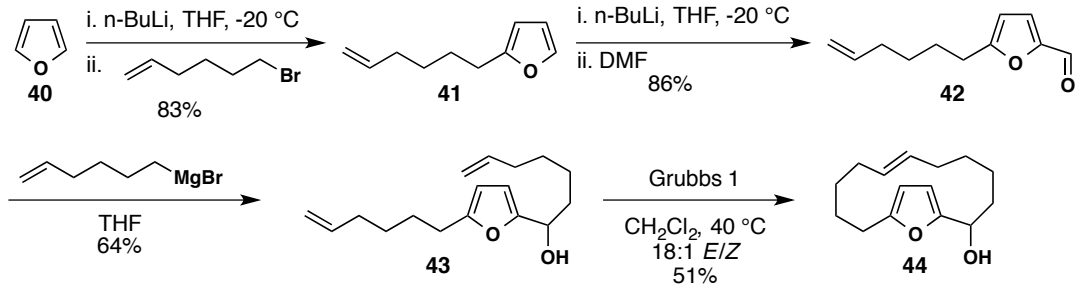
Scheme 7.8. Trauner's proposed biosynthetic pathway to coralloidolide F.

Coralloidolide F was first isolated in 1990 by Pietra and co-workers,[210] but thus far, no successful total synthesis has been reported. Noting the presence of the 4-hydroxycyclopentenone motif in coralloidolide F, our group proposed an alternative pathway to this natural product. We hypothesized that coralloidolide F (**2**) could be accessed via a Piancatelli rearrangement of bipinnatin J (**32**) to cyclopentenone **39**, which would yield the desired natural product upon epoxidation (Scheme 7.9). We approached Professor Trauner with this proposal and struck up a collaboration to achieve the synthesis of this elusive natural product. Thanks to a generous travel grant through UCSB's Materials Research Laboratory's International Center for Materials Research (ICMR) program, I was able to travel to the Ludwig-Maximilians Universität in Munich to conduct the proposed research in the Trauner laboratory.



Scheme 7.9. Our proposed synthesis of coralloidolide F via a Piancatelli rearrangement.

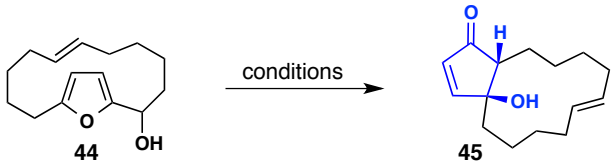
We commenced our studies with the synthesis of a model macrocyclic substrate. The model macrocycle was easily obtained via a four step protocol directly from furan (Scheme 7.10). Alkylation of furan (**40**) with 6-bromohex-1-ene[233] was followed by formylation with DMF and Grignard addition of the second alkyl chain to the other side of the furan. Finally, ring-closing metathesis (RCM) using Grubbs' first generation catalyst provided macrocyclic furylcarbinol **44** in 51% yield.[234]



Scheme 7.10. Synthesis of a macrocyclic model substrate.

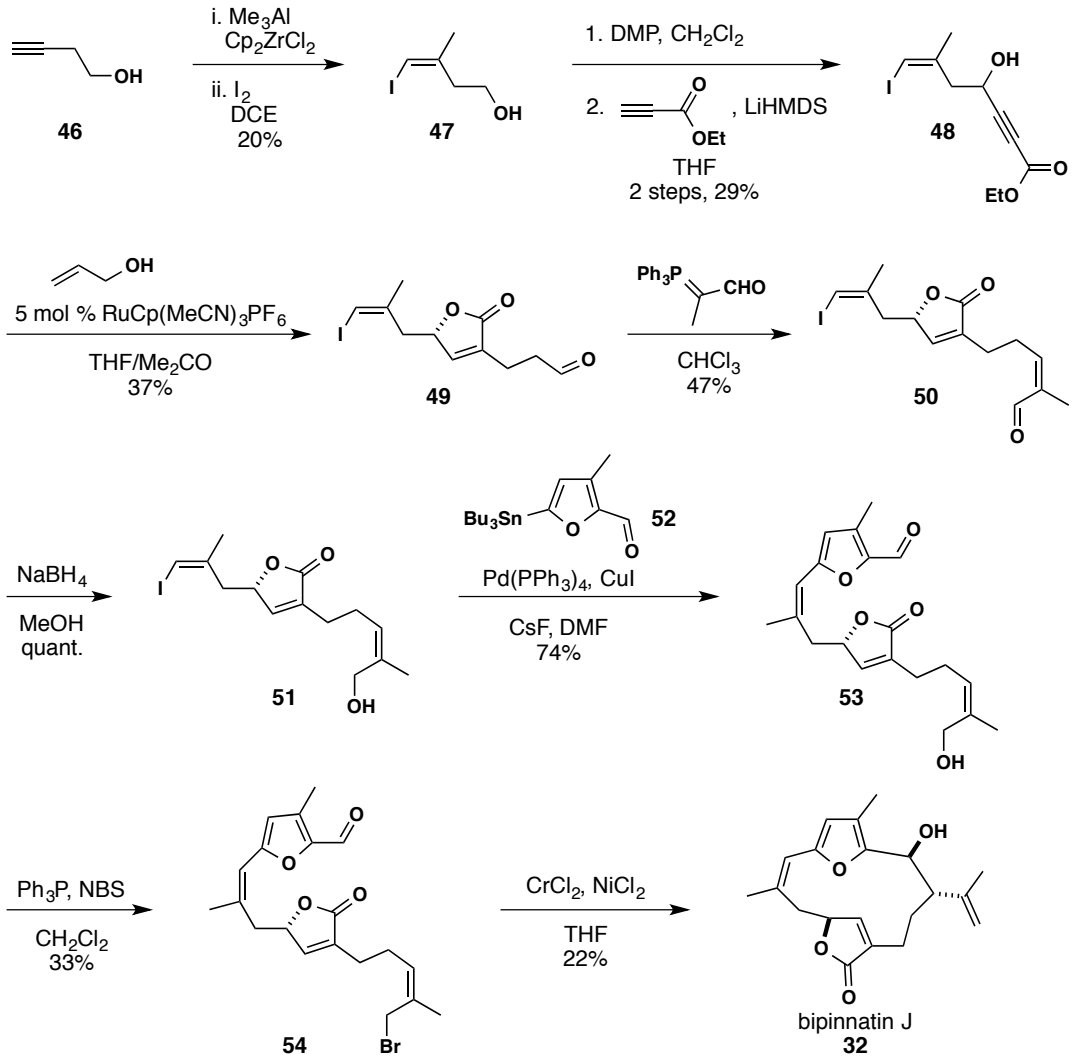
With macrocyclic furylcarbinol **44** in hand, we studied its rearrangement to 4-hydroxycyclopentenone **45**. To our disappointment, all efforts to effect the Piancatelli rearrangement of this macrocycle were unsuccessful (Table 7.2). Reactions using our standard aza-Piancatelli[78] rearrangement conditions or Piancatelli[52] and the Read Lab's [57] conditions did not result in formation of the desired product (Table 7.2, entries 1-4). Wu's conditions using $CuSO_4 \bullet 5H_2O$ (Table 7.2, entry 5),[235] rearrangement in 1,4-dioxane at reflux with $MgCl_2$ (Table 7.2, entry 7),[236] or reaction in a buffered NaOAc/AcOH (Table 7.2, entry 6) system all resulted in recovery of starting material. In some cases unidentified products possessing aldehyde protons were observed, but no desired product was formed. Speculating that ring-strain was the source of our difficulties, we also attempted the rearrangement of furylcarbinol **43**, but with no success.

Table 7.2. Efforts toward a macrocyclic Piancatelli rearrangement.



Entry	Catalyst (mol %)	Solvent	Temp (°C)	Yield (%)
1	$Dy(OTf)_3$ (30)	MeCN	80	--
2	$Dy(OTf)_3$ (10) TFA (5)	*t*BuOH/H_2O (5:1)	80	--
3	$ZnCl_2$ (100)	MeCN	60	--
4	$ZnCl_2$ (100)	Acetone	56	--
5	$CuSO_4$•$5H_2O$ (100)	PhMe	60	--
6	NaOAc, AcOH pH ~ 5	H_2O	µw	--
7	$MgCl_2$ (400)	H_2O/dioxane	reflux	--

While working in the Trauner laboratory, I also completed the total synthesis of bipinnatin J (**32**). The published synthesis protocol was successfully followed (Scheme 7.11).[232,237] The synthesis started from a zirconium mediated carboalumination of 3-butynol to afford (Z)-vinyl iodide **47** in 20% yield. Dess-Martin oxidation to the aldehyde followed by alkynilation provided **48** in 29% yield over two steps. Trost enyne reaction forming aldehyde **49** was followed by a Wittig reaction to form **50**. Reduction of aldehyde **50** was followed by Stille coupling to **52** to form allylic alcohol **53**. Appel reaction of the allylic alcohol furnished cyclization precursor **54** in 33% yield. Finally, the key Nozaki-Hiyama-Kishi cyclization was performed to give bipinnatin J (**32**) in 22% yield.



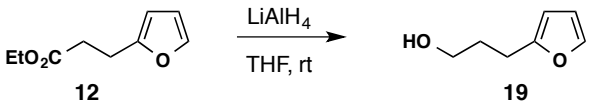
Scheme 7.11. Total synthesis of bipinnatin J.

Unfortunately we never had a chance to test the rearrangement of bipinnatin J to coralloidolide F. I am confident that further investigations on the Piancatelli rearrangement of the macrocyclic model substrate will be successful. Once optimal conditions have been determined, the rearrangement could be applied to bipinnatin J to give macrocyclic cyclopentenone **39** which, upon epoxidation, would result in the formation of coralloidolide F (**2**). Additionally, success of the rearrangement would open up the door to exploring a variety of rearrangements of furylcarbinols embedded in macrocycles.

7.4. Experimental Procedures

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using a Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Merck KGA). ^{1}H NMR spectra were recorded on Varian spectrometers (at 400, 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 MHz). Data for ^{13}C NMR spectra are reported as follows: shift (δ ppm), multiplicity and coupling constant (Hz). IR spectra were recorded on a Jasco FT/IR 4100 or a Perkin Elmer Spectrum 100 FT/IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the UC Santa Barbara Mass Spectrometry facility.

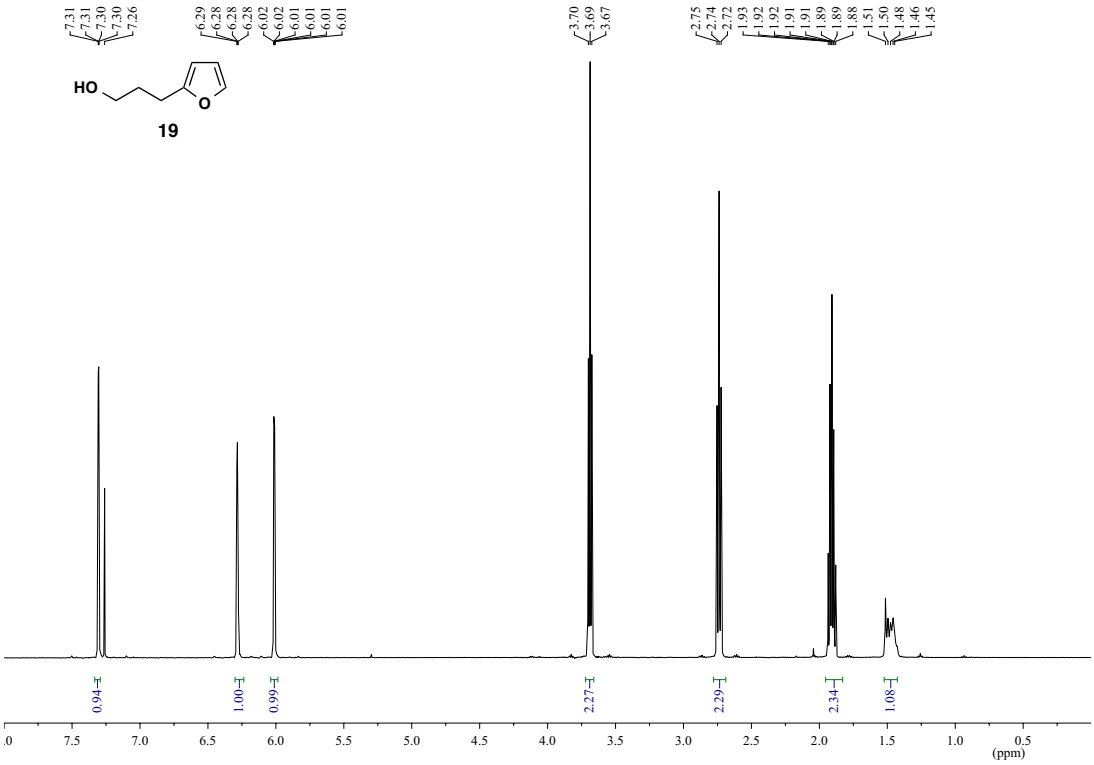
7.4.1. Efforts Toward the Total Synthesis of Cephalotaxine

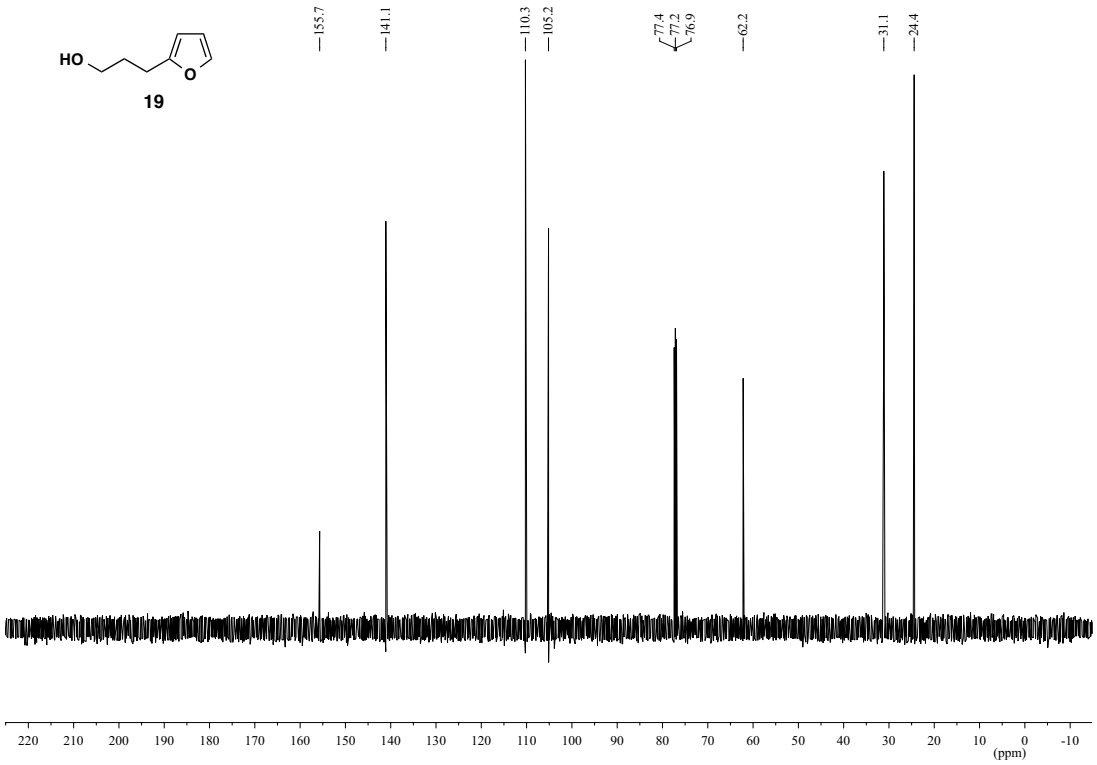


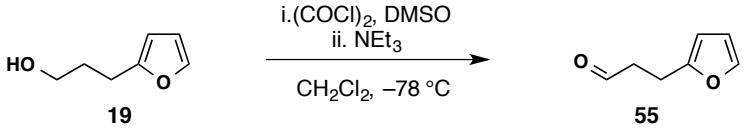
12 19

3-(Furan-2-yl)propan-1-ol (19): A solution of ethyl 3-(furan-2-yl)propanoate (**12**) (6.01 g, 35.7 mmol) in dry THF (180 mL) was treated with $LiAlH_4$ (1.36 g, 35.7 mmol) in several

small portions and stirred at rt for 1 h when so starting material was visible by TLC. The reaction was quenched via slow, dropwise addition of 1.36 mL H_2O, followed by 1.36 mL 3M NaOH, and finally 13.6 mL H_2O. After stirring at room temperature for 20 min, the suspension was filtered through Celite, washing with EtOAc (100 mL). The solvent was removed via rotary evaporation, and the product purified by flash column chromatography to afford alcohol **19** (3.47 mg, 77%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.30 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 6.01-5.99 (m, 1H), 3.69 (t, *J* = 6.3 Hz, 1H), 2.74 (t, *J* = 7.4 Hz, 1H), 1.94 – 1.88 (m, 1H), 1.53 – 1.34 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.7, 141.1, 110.3, 105.2, 62.2, 31.1, 24.4 ppm; **IR** (thin film) 3336, 2943, 2878, 1596, 1507, 1145, 1054, 1039, 1004 cm^{-1}; **MS** (EI+) *m/z* 126. 0678 (126. 0681 calcd for $C_7H_{10}O_2$ $[M]^{\bullet+}$).

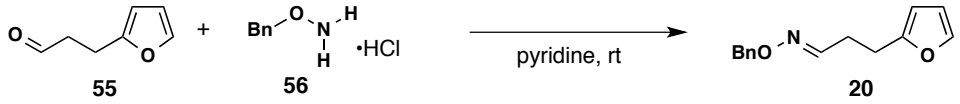






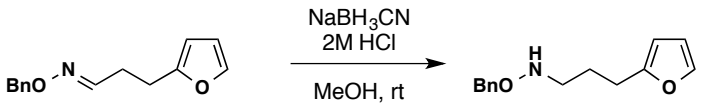
3-(Furan-2-yl)propanal (55): The Swern reagent was prepared by treating $(COCl)_2$ (3.45 mL, 40.7 mmol) in 250 mL dry CH_2Cl_2 at -78 °C with DMSO (3.86 mL, 54.3 mmol) via dropwise addition over 15 min. After 15 min, **19** (4.28 g, 33.9 mmol) was added dropwise as a solution in 20 mL dry CH_2Cl_2. The reaction was stirred at -78 °C for 45 min before it was quenched with NEt_3 (16.6 mL, 118.8 mmol) and allowed to come to rt. The resulting suspension was filtered through a pad of $MgSO_4$, washing with copious amounts of Et_2O. Due to the instability and volatility of the resulting aldehyde, the solvent was carefully removed via rotary evaporation, and the crude product **55** (3.01 g, 72%, clear oil) immediately subjected to the next transformation. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.83 (s,

1H), 7.31 (dd, *J* = 1.7, 0.9 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.02 (ddd, *J* = 3.4, 1.0, 1.0 Hz, 1H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.83 – 2.77 (m, 2H) ppm.



55 56 20

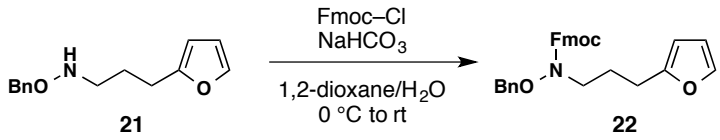
3-(Furan-2-yl)propanal *O*-benzyl oxime (20): A solution of **55** (3.01 g, 24.3 mmol) in 12 mL dry pyridine was treated with *O*-benzylhydroxylamine hydrochloride (**56**) (4.26 g, 26.7 mmol) and stirred at rt for 3 d. When the reaction was complete by TLC, it was diluted with Et_2O and H_2O, washed 3 x H_2O, 1 x brine. The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to afford oxime **20** (4.79 g, 86%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 5.8, 5.8 Hz, 0.6H), 7.38 – 7.34 (m, 4H), 7.33 – 7.29 (m, 2H), 6.74 (tdd *J* = 5.2, 5.2 Hz, 0.4H), 6.28 (ddd, *J* = 3.2, 3.2, 1.9 Hz, 1H), 6.04 – 5.99 (m, 3H), 5.13 (s, 1H), 5.07 (s, 1H), 2.83 (ddd, *J* = 10.9, 7.4, 7.4 Hz, 2H), 2.74 – 2.70 (m, 1H), 2.57 – 2.53 (m, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.5, 154.4, 151.0, 150.2, 141.4, 141.3, 138.1, 137.8, 128.5, 128.4, 128.1, 128.0, 127.9, 110.3, 110.3, 105.6, 105.6, 76.0, 75.8, 28.3, 25.4, 24.8, 24.5 ppm; **IR** (thin film) 3032, 2919, 2856, 1597, 1507, 1454, 1367, 1145, 1009 cm^{-1}; **MS** (ESI) *m/z* 252.0990 (252.1000 calcd for $C_{14}H_{15}NNaO_2$ $[MNa]^+$).



20 21

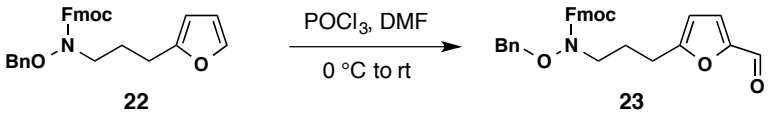
***O*-Benzyl-*N*-(3-(furan-2-yl)propyl)hydroxylamine (21):** A solution of **20** (412.5 mg, 1.80 mmol) in 13 mL MeOH was treated with $NaBH_3CN$ (181.3 mg, 2.89 mmol), followed

by dropwise addition of 2.7 M methanolic HCl (2.7 mL). The reaction was stirred at rt until complete by TLC (18 h). The reaction was quenched with 3M NaOH until a pH of 9 was reached, then diluted with CH_2Cl_2 and extracted (3 x CH_2Cl_2). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to afford hydroxylamine **21** (389.0 mg, 93%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38 – 7.28 (m, 6H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.99 – 5.98 (m, 1H), 5.58 (s, 1H), 4.71 (s, 2H), 2.98 (t, *J* = 7.0 Hz, 2H), 2.69 (t, *J* = 7.5 Hz, 2H), 1.88 (dt, *J* = 14.8, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.8, 141.0, 138.1, 128.5, 128.5, 127.9, 110.2, 105.1, 76.4, 51.5, 26.0, 25.7 ppm; **IR** (thin film) 2913, 2856, 1596, 1507, 1454, 1362, 1145, 1005, 915 cm^{-1}; **MS** (ESI) *m/z* 254.1147 (254.1157 calcd for $C_{14}H_{17}NNaO_2$ $[MNa]^+$).



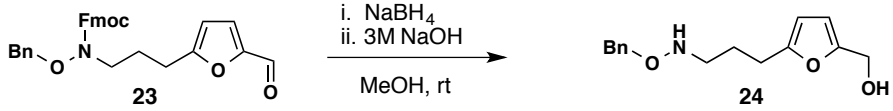
(9*H*-Fluoren-9-yl)methyl (benzyloxy)(3-(furan-2-yl)propyl)carbamate (22): A solution of **21** (2.64 g, 11.4 mmol) in H_2O/dioxane (2:1) (31 mL) was treated with $NaHCO_3$ (1.02 g, 22.8 mmol) and cooled to 0 °C for 10 min. Then, a solution of Fmoc-Cl (2.96 g, 11.4 mmol) in 30 mL dioxane was added via dropwise addition over 10 min. The reaction was allowed to come to rt for 2.5 h, then diluted with H_2O and EtOAc. Extracted with EtOAc (3 x 20 mL), the combined organic layers were dried over $MgSO_4$, filtered and the solvent removed via rotary evaporation. The product was purified via flash column chromatography to afford **22** (4.58 g, 89%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.35 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.30 – 7.27 (m, 4H), 7.27 – 7.21 (m, 4H), 6.23 – 6.21 (m, 1H), 5.92 (ddd, *J* = 3.4, 1.0, 1.0 Hz, 1H), 4.67 (s, 2H), 4.57 (d,

J = 1.0 Hz, 1H), 4.56 (d, J = 1.0 Hz, 1H), 4.22 (t, J = 6.3 Hz, 1H), 3.39 (dd, J = 7.2, 7.2 Hz, 2H), 2.54 (dd, J = 7.5, 7.5 Hz, 2H), 1.84 (dddd, J = 7.4, 7.4, 7.4, 7.4 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 157.3, 155.2, 143.9, 141.5, 141.1, 135.4, 129.4, 128.7, 128.6, 127.9, 127.3, 125.1, 120.1, 110.3, 105.2, 77.2, 67.4, 49.4, 47.5, 25.5, 25.4 ppm; **IR** (thin film) 3083, 2947, 2879, 1701, 1450, 1402, 1283, 1168, 1098, 1005 cm^{-1}; **MS** (ESI) *m/z* 476.1834 (476.1838 calcd for $C_{29}H_{27}NNaO_4$ $[MNa]^+$).

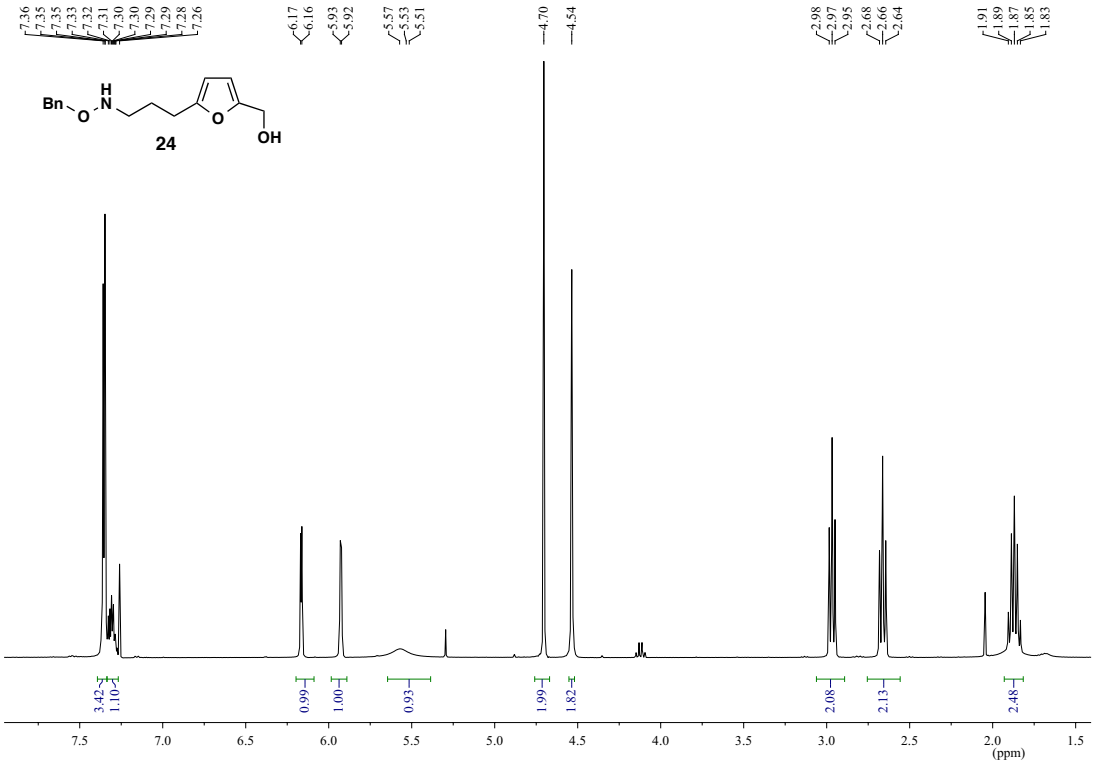


(9*H*-Fluoren-9-yl)methyl (benzyloxy)(3-(5-formylfuran-2-yl)propyl)carbamate (23): To prepare the Vilsmeier-Haack reagent, phosphorous oxychloride (2.16 mL, 23.1 mmol) was slowly added to DMF (2.1 mL, 27.2 mmol) at 0 °C via dropwise addition. After complete addition, the mixture was heated at 85 °C for 1 h to ensure complete formation of the reagent. The flask was cooled to 0 °C for the addition of a solution of **22** (4.56 g, 10.1 mmol) in 3 mL dry CH_2Cl_2. The reaction was allowed to come to rt, and stirred for 3 h. The reaction was transferred to an Erlenmeyer flask, quenching with water, then $NaHCO_3$ until the evolution of bubbles ceased. The mixture was diluted with EtOAc and extracted (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed. The product was purified via flash column chromatography to give **23** (4.21 g, 87%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.62 (d, J = 7.5 Hz, 2H), 7.39 (dd, J = 7.5, 7.5 Hz, 2H), 7.35 – 7.28 (m, 5H), 7.27 – 7.22 (m, 2H), 7.14 (d, J = 3.5 Hz, 1H), 6.18 (d, J = 3.5 Hz, 1H), 4.67 (s, 2H), 4.65 (s, 1H), 4.64 (s, 1H), 4.26 (t, J = 6.0 Hz, 1H), 3.39 (dd, J = 6.9, 6.9 Hz, 2H), 2.62 (dd, J = 7.6, 7.6 Hz, 2H), 1.87 (dddd, J = 7.3, 7.3, 7.3, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 177.1, 162.7,

157.2, 152.1, 143.8, 141.6, 135.3, 129.4, 128.8, 128.6, 127.9, 127.3, 125.0, 120.2, 109.1, 77.1, 67.3, 49.1, 47.5, 25.7, 24.9 ppm; **IR** (thin film) 3084, 2948, 2880, 2820, 1699, 1672, 1516, 1450, 1398, 1279, 1167, 1097, 1021, 961 cm^{-1}; **MS** (ESI) *m/z* 504.1764(504.1787 calcd for $C_{30}H_{27}NNaO_5$ $[MNa]^+$).



(5-(3-((Benzyloxy)amino)propyl)furan-2-yl)methanol (24): A solution of **23** (1071 mg, 2.22 mmol) in 64 mL MeOH was treated with $NaBH_4$ (134.6 mg, 3.56 mmol) and stirred at rt. The reaction was complete after 10 min as determined by TLC. The reaction was quenched with H_2O, followed by addition of 3 M NaOH. After 40 min, the reaction was complete by TLC and was extracted 3 x EtOAc (30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **24** (563.3 mg, 97%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 4.4 Hz, 4H), 7.34 – 7.27 (m, 1H), 6.17 (d, *J* = 3.1 Hz, 1H), 5.93 (d, *J* = 3.1 Hz, 1H), 5.57 (bs, 1H), 4.70 (s, 2H), 4.54 (s, 2H), 2.97 (dd, *J* = 7.0, 7.0 Hz, 2H), 2.66 (dd, *J* = 7.5, 7.5 Hz, 2H), 1.87 (dddd, *J* = 7.3, 7.3, 7.3, 7.3 Hz, 2H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 156.0, 152.5, 138.0, 128.5, 128.5, 128.0, 108.6, 105.9, 76.4, 57.7, 51.4, 25.8, 25.8 ppm; **IR** (thin film) 3348, 3257, 3031, 2918, 2862, 1560, 1454, 1362, 1208, 1009 cm^{-1}; **MS** (ESI) *m/z* 284.1253 (284.1263 calcd for $C_{15}H_{19}NNaO_3$ $[MNa]^+$).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7.28
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6.16
5.93
5.92
5.57
5.53
5.51
4.70
4.54
2.98
2.97
2.95
2.68
2.66
2.64
1.91
1.89
1.87
1.85
1.83
Bn
O
H
N
O
OH
24
3.42
1.10
0.99
1.00
0.93
1.99
1.82
2.08
2.13
2.48
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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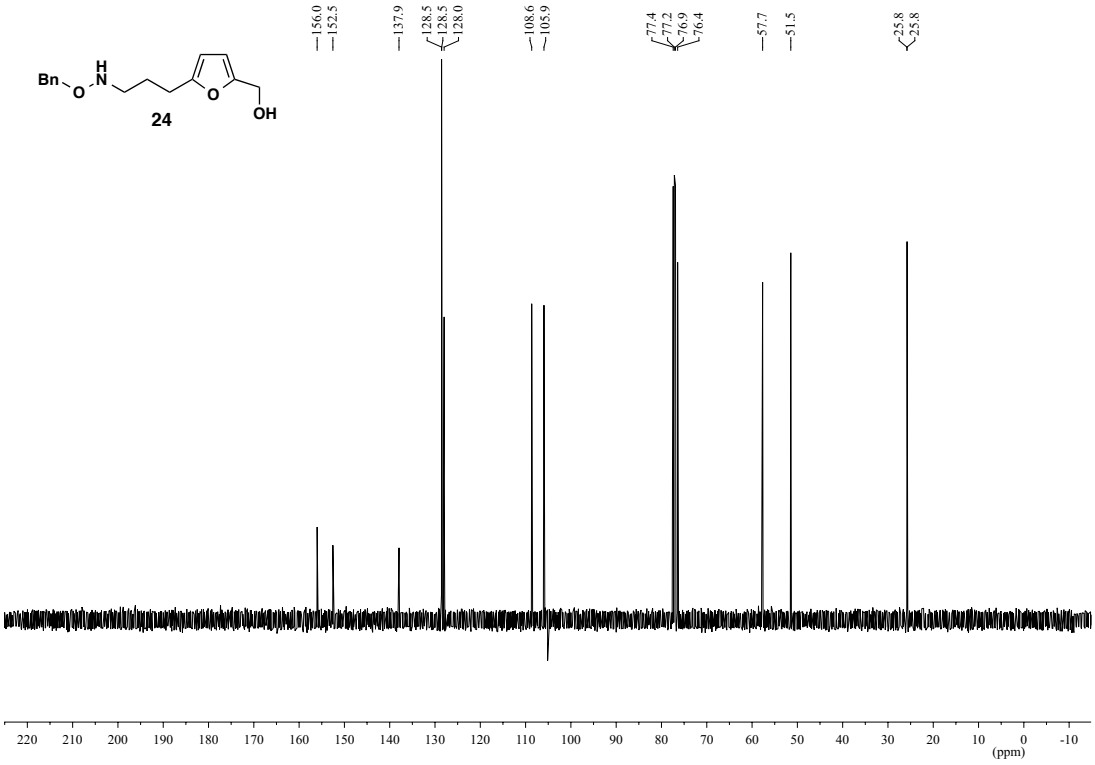
3.0
2.5
2.0
1.5
(ppm)


156.0
152.5
137.9
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128.5
128.0
108.6
105.9
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77.2
76.9
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51.5
25.8
25.8
Bn
O
H
N
O
OH
24
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
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50
40
30
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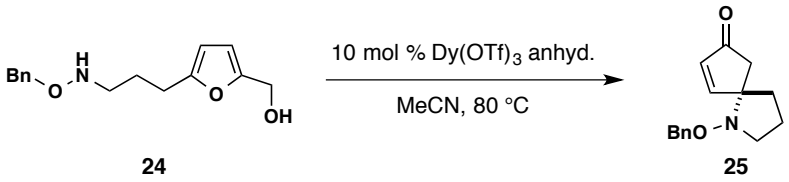
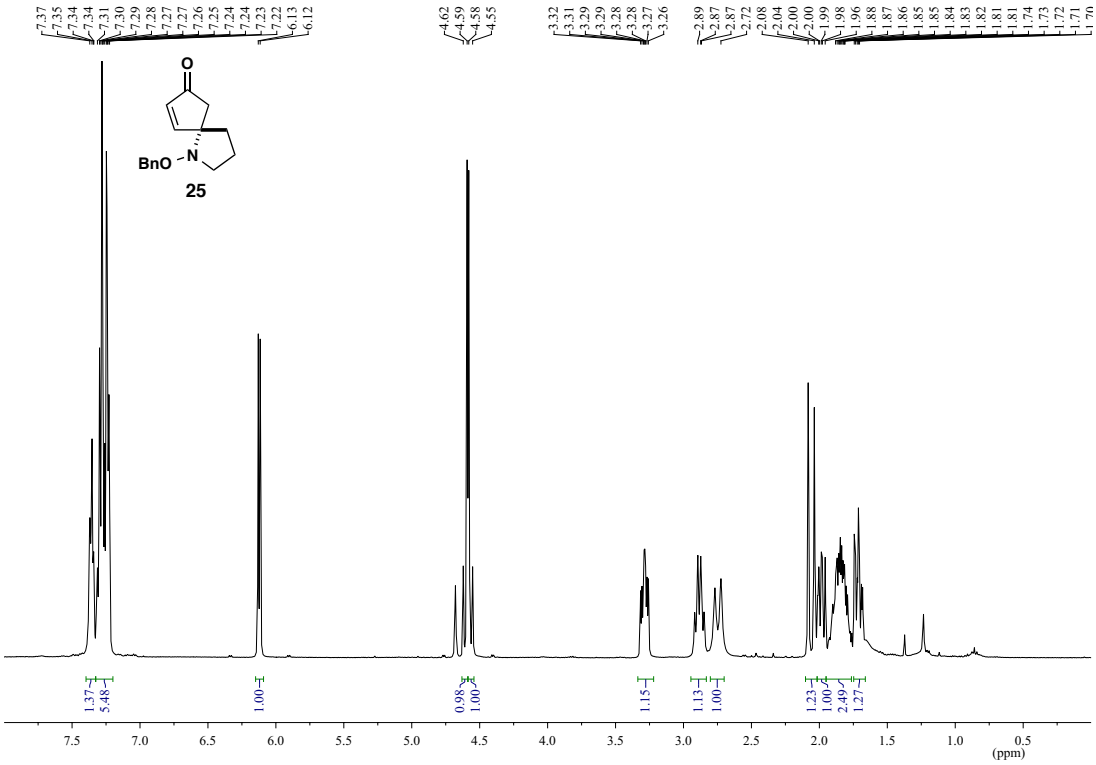
10
0
-10
(ppm)



24 25

1-(Benzyloxy)-1-azaspiro[4.4]non-8-en-7-one (25): A solution of **24** (50.0 mg, 0.19 mmol) in 20 mL dry MeCN was treated with anhydrous $Dy(OTf)_3$ (11.7 mg, 0.019 mmol) and heated in a preheated oil bath at 80 °C. The reaction was complete by TLC after approximately 6 h, although reaction times varied, and in some cases, an additional 10 mol % $Dy(OTf)_3$ was added to push the reaction to completion. The flask was removed from the oil bath and the reaction quenched with saturated $NaHCO_3$ (20 mL) and diluted with EtOAc. The mixture was extracted 3x EtOAc (20 mL) and the combined organic phases were dried over $MgSO_4$, filtered and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **25** (20.0 mg, 43%) as a light yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 1H), 7.33 – 7.20 (m, 5H), 6.12 (d, *J* = 5.6 Hz, 1H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 3.29 (ddd, *J* = 10.3, 8.4, 4.2 Hz, 1H), 2.88 (ddd, *J* = 10.1, 9.7, 9.7 1H), 2.75 (d, *J* = 18.0 Hz, 1H), 2.06 (d, *J* = 18.0 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.94 – 1.76 (m, 2H), 1.71 (ddd, *J* = 12.5, 9.0, 3.7 Hz, 1H) ppm; **^{13}C NMR** (125 MHz, $CDCl_3$) δ 207.7, 165.8, 137.6, 134.9, 128.8, 128.4, 128.0, 76.5, 65.5, 54.0, 42.0, 33.6, 19.7 ppm; **IR** (thin film) 3063, 3031, 2933, 2865, 1713, 1454, 1186, 1041, 993 cm^{-1}; **MS** (ESI) *m/z* 266.1145 (266.1157 calcd for $C_{15}H_{17}NNaO_2$ $[MNa]^+$).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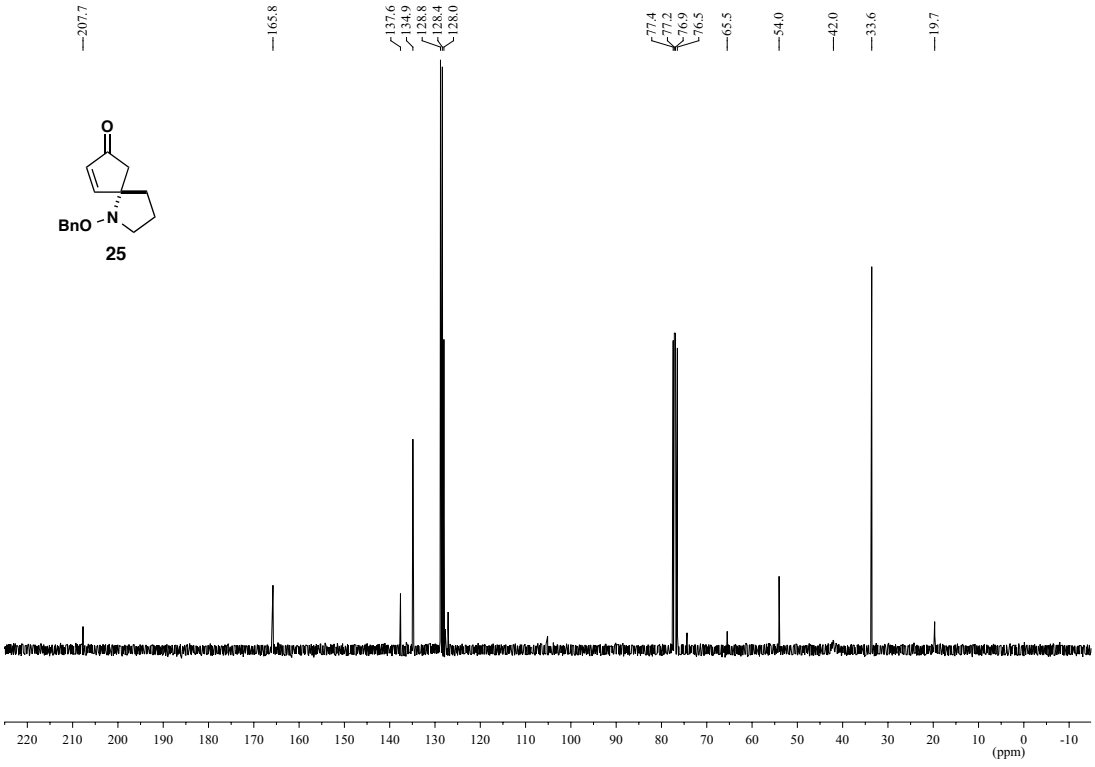
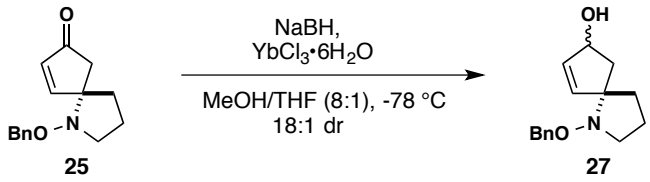
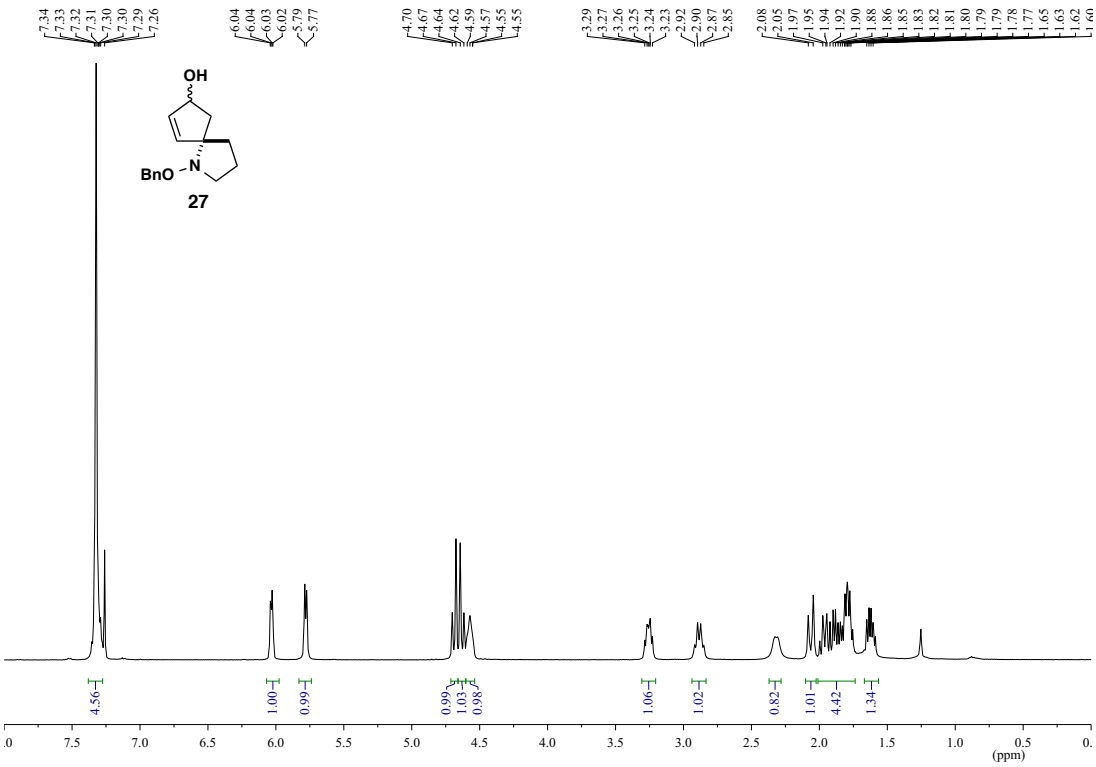
N
O
25
(ppm)

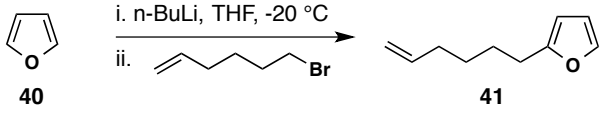

BnO
N
O
25
(ppm)



1-(Benzyloxy)-1-azaspiro[4.4]non-8-en-7-ol (27): A solution of **25** (17.6 mg, 0.072 mmol) in MeOH (1.8 mL) and THF (0.2 mL) was treated with $YbCl_3 \bullet 6H_2O$ (56.1 mg, 0.14 mmol) and stirred at rt for 20 min. The solution was cooled to –78 °C and subsequently treated with $NaBH_4$ (5.4 mg, 0.14 mmol) and stirred at this temperature until the reaction was complete by TLC. The reaction was quenched with saturated NH_4Cl, allowed to come to rt and then extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford allylic alcohol **27** (16.5 mg, 95%, 18:1 dr) as a brown yellow oil. *Major:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 5H), 6.03 (dd, *J* = 5.6, 2.4 Hz, 1H), 5.78 (d, *J* = 5.5 Hz, 1H), 4.69 (d, *J* = 10.7 Hz, 1H), 4.63 (d, *J* = 10.7 Hz, 1H), 4.57 (dd, *J* = 8.2, 8.2 Hz, 1H), 3.26 (ddd, *J* = 9.8, 6.5 Hz, 1H), 2.88 (ddd, *J* = 9.1, 9.1, 9.1 Hz, 1H), 2.32 (d, *J* = 11.9 Hz, 1H), 2.06 (d, *J* = 14.4 Hz, 1H), 2.01 – 1.74 (m, 4H), 1.62 (ddd, *J* = 12.9, 6.7, 6.7 Hz, 1H) ppm.



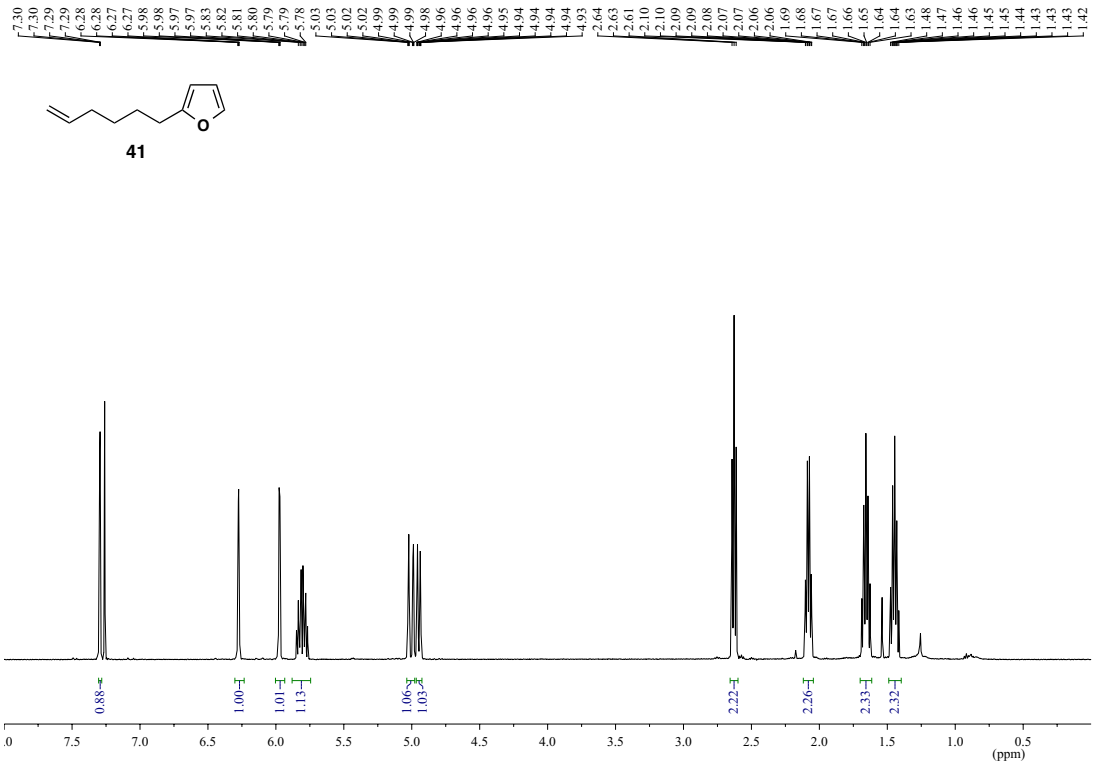
7.4.2. Efforts Toward the Total Synthesis of Coralloidolide F

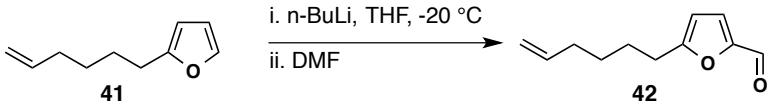


40 41

2-(Hex-5-en-1-yl)furan (41): A solution of furan (195 µL, 2.69 mmoL) in 12 mL dry THF was treated with *n*-BuLi (2.5 M in hexanes) (1.08 mL, 2.69 mmol) at -20 °C. After 1h below 0 °C, 6-bromo-1-hexene (300 µL, 2.24 mmol) was added to the solution at -20 °C, and the reaction allowed to come to rt over 2 h. The reaction was quenched with saturated NH_4Cl solution (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **41**, which is inseparable from unreacted 6-bromo-1-hexene (277.7 mg, 83%) as a clear oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.28 (dd, *J* = 3.1, 1.9 Hz, 1H), 5.97 (dd, *J* = 3.2, 1.2 Hz, 1H),

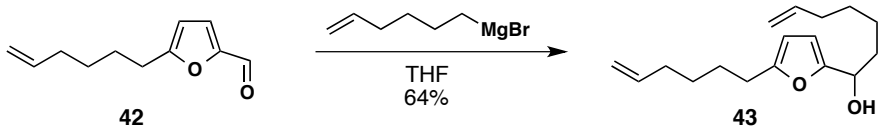
5.81 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.01 (dddd, *J* = 17.1, 1.7, 1.7 Hz, 1H), 4.95 (dddd, *J* = 10.3, 2.3, 1.2, 1.2 Hz, 1H), 2.63 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.13 – 2.03 (m, 2H), 1.66 (dddd, *J* = 7.6, 7.6, 7.6, 7.6 Hz, 2H), 1.45 (dddd, *J* = 7.6, 7.6, 7.6, 7.6 Hz, 2H) ppm.





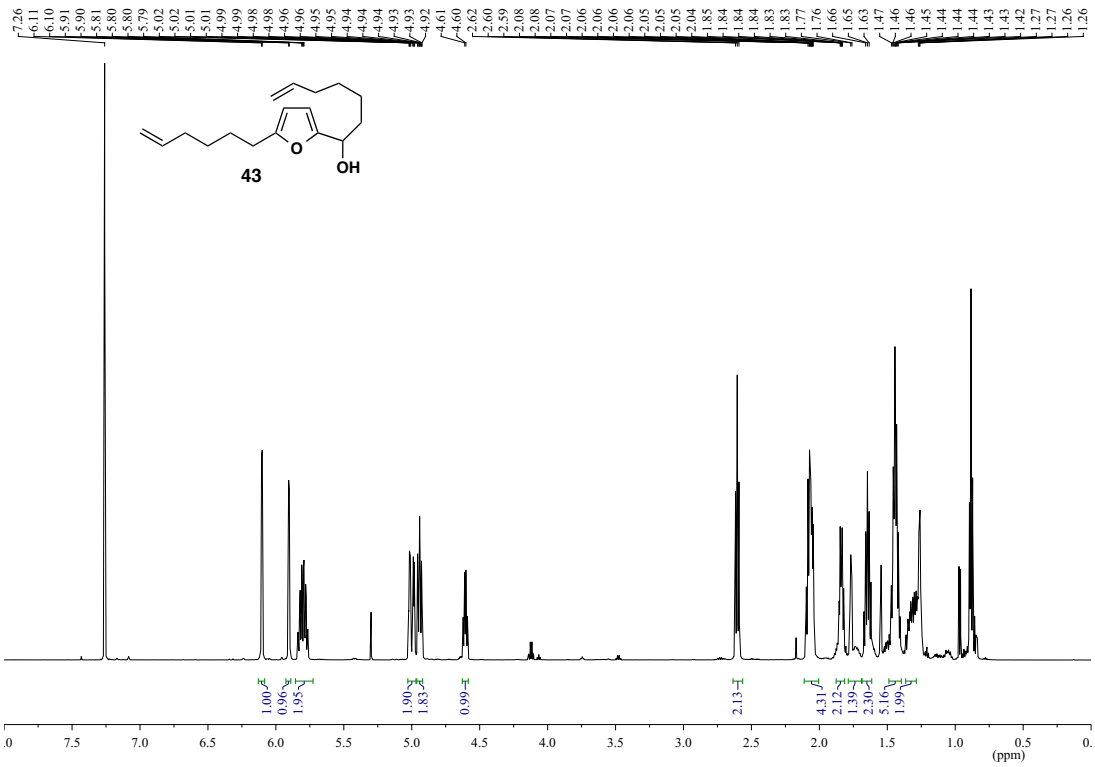
5-(Hex-5-en-1-yl)furan-2-carbaldehyde (42): A solution of **41** (729.3 mg, 4.86 mmoL) in 170 mL dry THF was treated with *n*-BuLi (2.2 M in hexanes) (4.41 mL, 9.72 mmol) at -20 °C. After 1h below 0 °C, DMF (720 µL, 9.72 mmol) was added to the solution at -20 °C, and the reaction allowed to come to rt over 2 h. The reaction was quenched with saturated NH_4Cl solution (100 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **42** (429.0 mg, 54%) as a clear

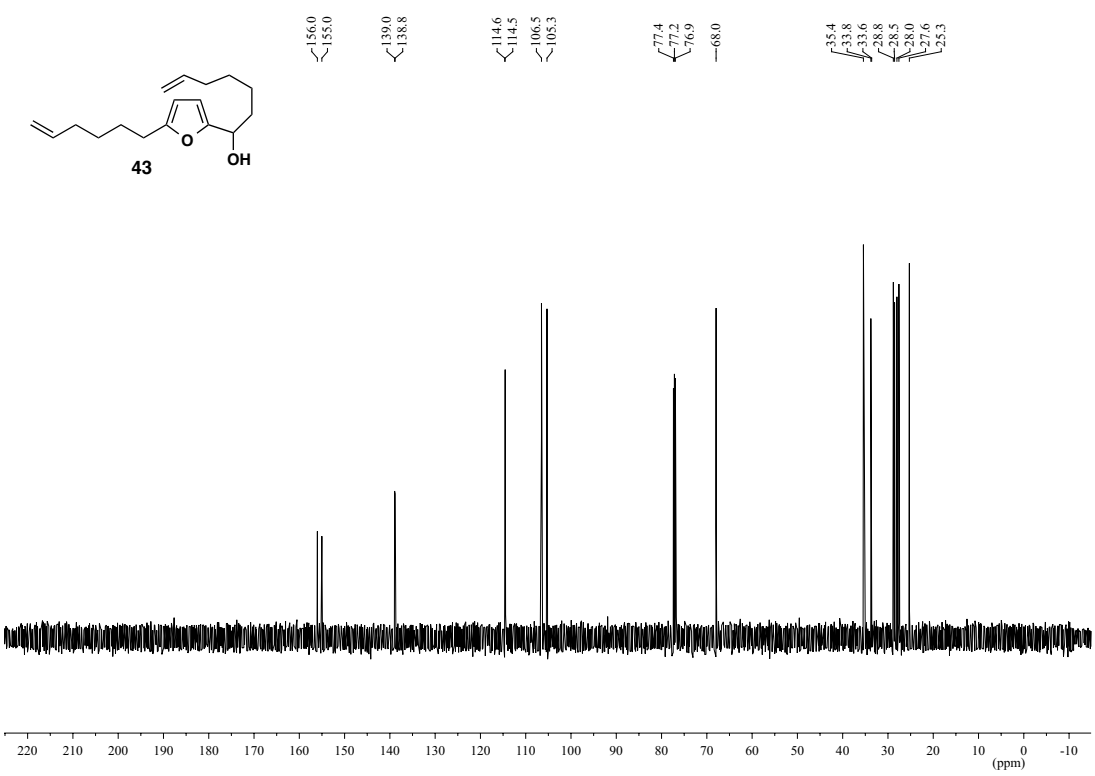
oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.17 (d, *J* = 3.5 Hz, 1H), 6.23 (d, *J* = 3.5 Hz, 1H), 5.79 (dddd, *J* = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.01 (dddd, *J* = 17.1, 1.7, 1.7, 1.7 Hz, 1H), 4.96 (dddd, *J* = 10.1, 2.1, 1.2, 1.2 Hz, 1H), 2.73 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.76 – 1.67 (m, 2H), 1.49 – 1.41 (m, 2H) ppm.

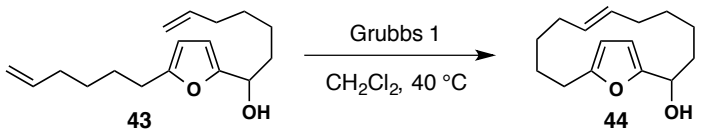


42 **43**

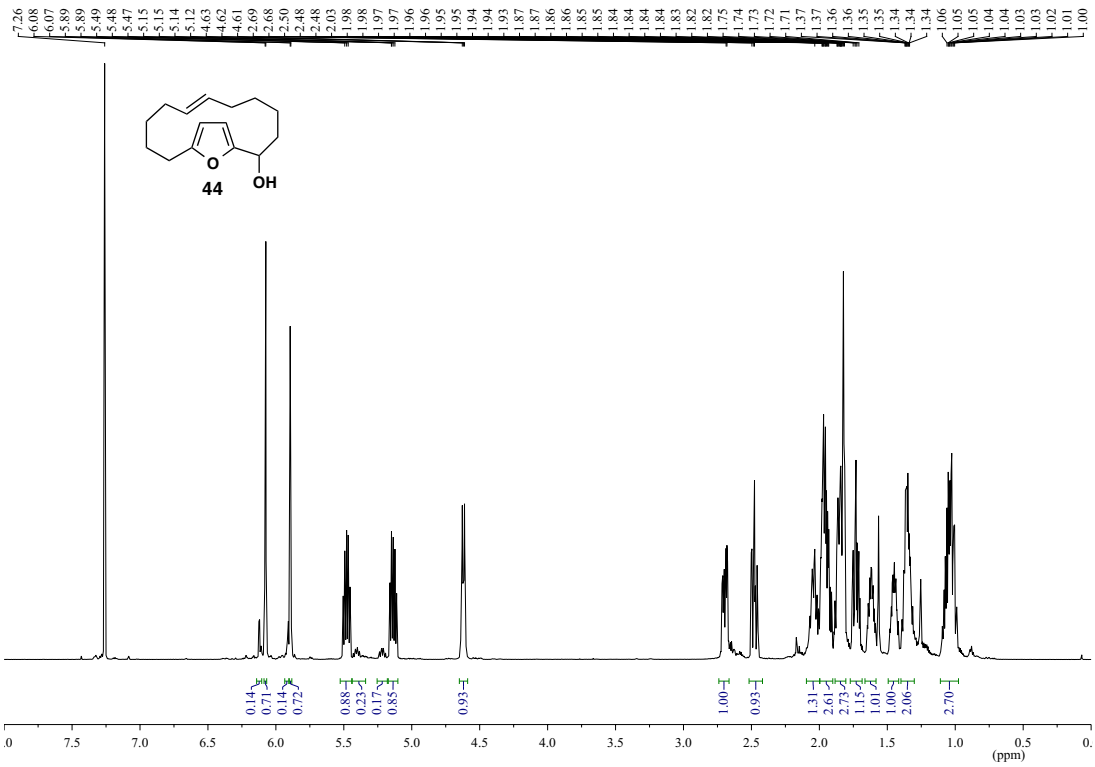
1-(5-(Hex-5-en-1-yl)furan-2-yl)hept-6-en-1-ol (43): The Grignard reagent was prepared by combining iodine-activated Mg (79.5 mg, 3.27 mmol) with 6-bromo-1-hexene (380 μL, 2.84 mmol) in 10 mL dry THF and stirring at rt for 4 h. The Grignard reagent was then added to a solution of **42** (358.1 mg, 2.18 mmol) in 10 mL dry THF and the reaction stirred for 4 h until no starting material was visible by TLC. The reaction was quenched with saturated NH_4Cl, extracted 3 x Et_2O (20 mL), and the combined organic layers were dried over $MgSO_4$ before filtering and removing the solvent via rotary evaporation. The product was purified via flash column chromatography to give **43** (358.4 mg, 63%) as a clear oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.10 (d, *J* = 3.0 Hz, 1H), 5.90 (d, *J* = 3.0 Hz, 1H), 5.84 – 5.76 (m, 2H), 5.03 – 4.97 (m, 2H), 4.96 – 4.91 (m, 2H), 4.61 (ddd, *J* = 6.8, 6.8, 5.0 Hz, 1H), 2.60 (dd, *J* = 7.6, 7.6 Hz, 2H), 2.11 – 2.03 (m, 4H), 1.84 (dddd, *J* = 11.1, 5.6, 3.2, 3.2 Hz, 2H), 1.78 – 1.74 (m, 1H), 1.64 (dddd, *J* = 7.6, 7.6, 7.6, 7.6 Hz, 2H), 1.50 – 1.39 (m, 4H), 1.36 – 1.23 (m, 2H) ppm. **^{13}C NMR** (150 MHz, $CDCl_3$) δ 156.0, 155.0, 139.0, 138.8, 114.6, 114.5, 106.5, 105.3, 68.0, 35.4, 33.8, 33.6, 28.8, 28.5, 28.0, 27.6, 25.3 ppm.


43
OH
(ppm)


43
OH
(ppm)



(*E*)-1(2,5)-Furanacyclododecaphan-7-en-2-ol (44): A solution of **43** (100.0 mg, 0.38 mmol) in 130 mL dry, degassed CH_2Cl_2 was treated with Grubbs 1 (47.0 mg, 0.057 mmol) and heated at reflux for 16 h. The reaction was monitored by removing aliquots and examining them by ^{1}H NMR to determine completion of the reaction. If the reaction had not gone to completion, additional catalyst was added. Once the reaction was complete, the solvent was removed and the product was purified by flash column chromatography to give **44** (45.4 mg, 51%, 8:1 *E*/*Z*) as a light brown solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ6.06 (d, *J* = 3.0 Hz, 1H), 5.88 (d, *J* = 2.9 Hz, 1H), 5.46 (dtt, *J* = 15.0, 7.7, 1.3 Hz, 1H), 5.12 (ddd, *J* = 15.2, 7.7, 6.3 Hz, 1H), 4.60 (ddd, *J* = 9.3, 4.3, 4.3 Hz, 1H), 2.68 (ddd, *J* = 15.0, 6.8, 3.1 Hz, 1H), 2.46 (ddd, *J* = 14.5, 11.1, 3.0 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.98 – 1.88 (m, 3H), 1.87 – 1.78 (m, 3H), 1.71 (tt, *J* = 12.7, 4.4 Hz, 1H), 1.60 (dddq, *J* = 15.7, 9.4, 6.3, 3.1 Hz, 1H), 1.47 – 1.40 (m, 1H), 1.38 – 1.29 (m, 2H), 1.09 – 0.96 (m, 3H) ppm.


7.26
6.08
6.07
5.89
5.89
5.49
5.48
5.47
5.15
5.15
5.14
5.12
4.63
4.62
4.61
2.69
2.68
2.50
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1.06
1.05
1.05
1.04
1.04
1.03
1.03
1.02
1.01
1.00
O
OH
44
0.14
0.71
0.14
0.72
0.88
0.23
0.17
0.85
0.93
1.00
0.93
1.31
2.61
2.73
1.15
1.01
1.00
2.06
2.70
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

8. A Molecular Rearrangement of Oxaspirocycles to Fused Bicycles

8.1. The Intramolecular Oxa-Piancatelli Rearrangement

With the widespread presence of the aminocyclopentenone motif in natural products and pharmaceutically active compounds, much of my research focus has centered on the development of the aza-Piancatelli rearrangement. Throughout the course of our studies, however, we also developed an interest in expanding on the original Piancatelli rearrangement.[57] Having already developed the aza-Piancatelli rearrangement with anilines[78] as well as the intramolecular aza-Piancatelli rearrangement to access azaspirocycles,[138] we became intrigued by the possibility of accessing oxaspirocycles **1**. Oxaspirocycles are well represented in natural products, such as sieboldine A (**2**)[238,239] and heliespirone C (**3**),[240] and are a desirable synthetic motif (Figure 8.1).

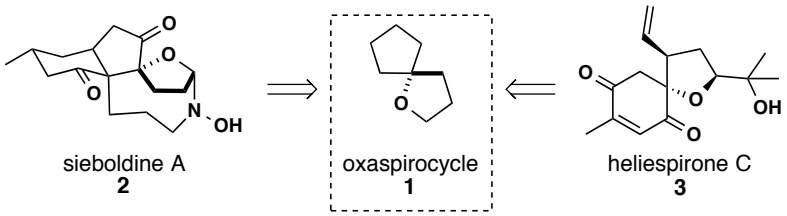
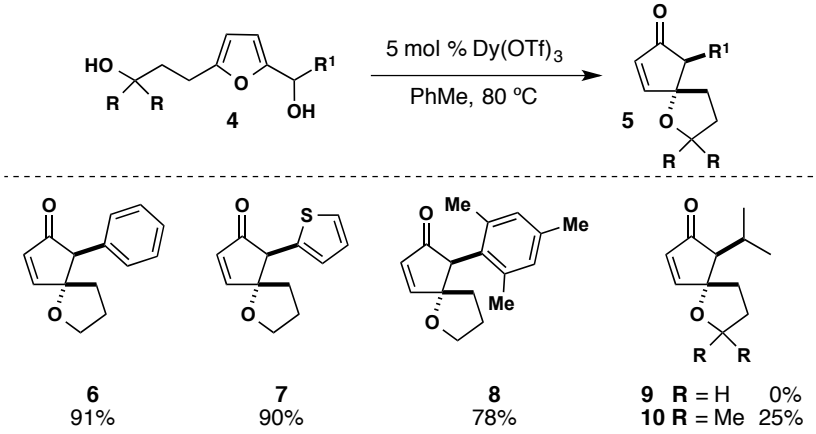


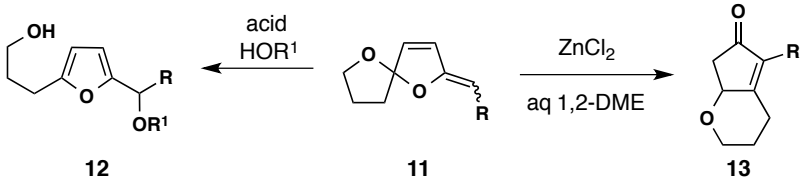
Figure 8.1. Oxaspirocycles in natural products.

Despite the obvious value of such an intramolecular Piancatelli rearrangement, it was not until Dr. Leoni Palmer's efforts that an intramolecular oxa-Piancatelli rearrangement was realized.[139] The rearrangement furylcarbinols **4** was catalyzed by $Dy(OTf)_3$ in toluene at 80 °C and was utilized for the synthesis of a variety of oxaspirocyclic cyclopentenones **5** (Scheme 8.1). Prior to the development of this protocol, access to the spirocyclic cyclopentenones had been elusive. Wu and co-workers have studied reactions of enol ether

spiroketals **11** extensively, but only observed formation of the ring-opened furan derivatives **12** or fused bicycles **13** (Scheme 8.2).[241–243]



Scheme 8.1. Select scope of the dysprosium catalyzed oxa-Piancatelli rearrangement.



Scheme 8.2. Previous work with oxaspirocycle precursors.

Having established that the intramolecular oxa-Piancatelli rearrangement to access oxaspirocyclic cyclopentenones is a possibility, we were interested in examining whether spirocycles **5** could be isomerized to oxabicycles **13**. Several groups have studied the migration of the hydroxyl group to the more highly substituted cyclopentenone. Piancatelli and co-workers described an intramolecular process facilitated by Al_2O_3 for the synthesis of prostaglandin alkaloids,[244] while Stork and West described a two-step hydration-dehydration process with strong base (Figure 8.2).[242,245] The $ZnCl_2$ catalyzed rearrangement of **17** to **13** described by Wu is proposed to proceed via addition of the tethered alcohol followed by elimination of the hydroxyl group of **18** (Scheme 8.3).[242,243]

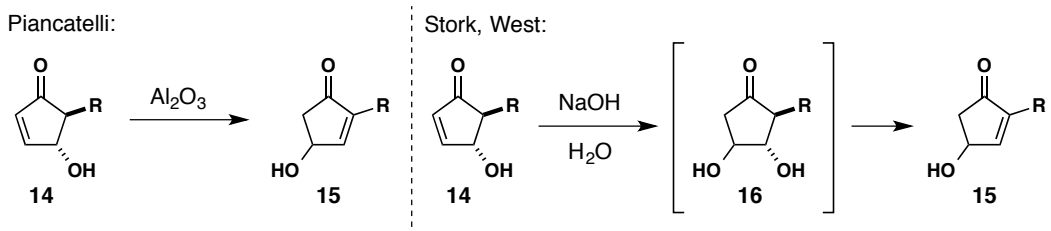
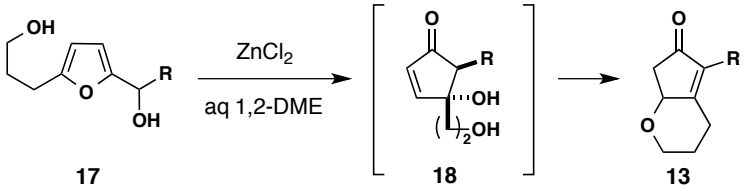


Figure 8.2. Migration of the alcohol functional group.



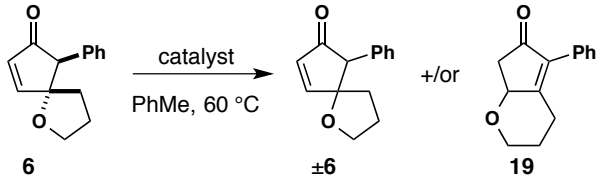
Scheme 8.3. Wu's method to access to fused oxabicycles via 4-hydroxycyclopentenones.

8.2. Molecular Rearrangement of Oxaspirocycles to Fused Oxabicycles

We commenced our studies with the proposed molecular rearrangement of spirocycle **6** to oxabicycle **19** (Table 8.1). Initially, we attempted the conversion between the two bicycles using reaction conditions previously described by Wu et al., ($ZnCl_2$ in refluxing aqueous 1,2-dimethoxyethane (DME)).[242,243] No change to the spirocycle was observed and **6** was recovered from the reaction conditions in good yield and with little to no decomposition. Treatment of the spirocycle with basic alumina resulted in complete erosion of the *trans* selectivity through epimerization; however, no desired rearrangement was observed. Interestingly, other bases, such as DMAP, Hünigs base, cesium carbonate, sodium carbonate and sodium phosphates resulted in only recovered starting material. Based on these experiments, we further examined the use of other acids (Table 8.1, entries 3 – 7), which also resulted in epimerization of the *trans*-substituted spirocycle to a mixture of *trans* and *cis* substitution to varying degrees along with other unidentified minor reaction components. Treatment of spirocycle **6** with sulfuric acid resulted in its decomposition

within minutes. A notable exception was *p*-TSA, which showed the fused cyclopentenone **19** in roughly 50% conversion after 24 hours. We were pleased to find that the acidic ion-exchange resin Amberlyst®15 could be used to carry out the same transformation in a cleaner and more efficient manner; treatment of **6** with acidic Amberlyst®15 provided the fused bicycle **19** in excellent yield (Table 8.1, entry 8).

Table 8.1. Optimization studies for the molecular rearrangement.



6 ±6 19

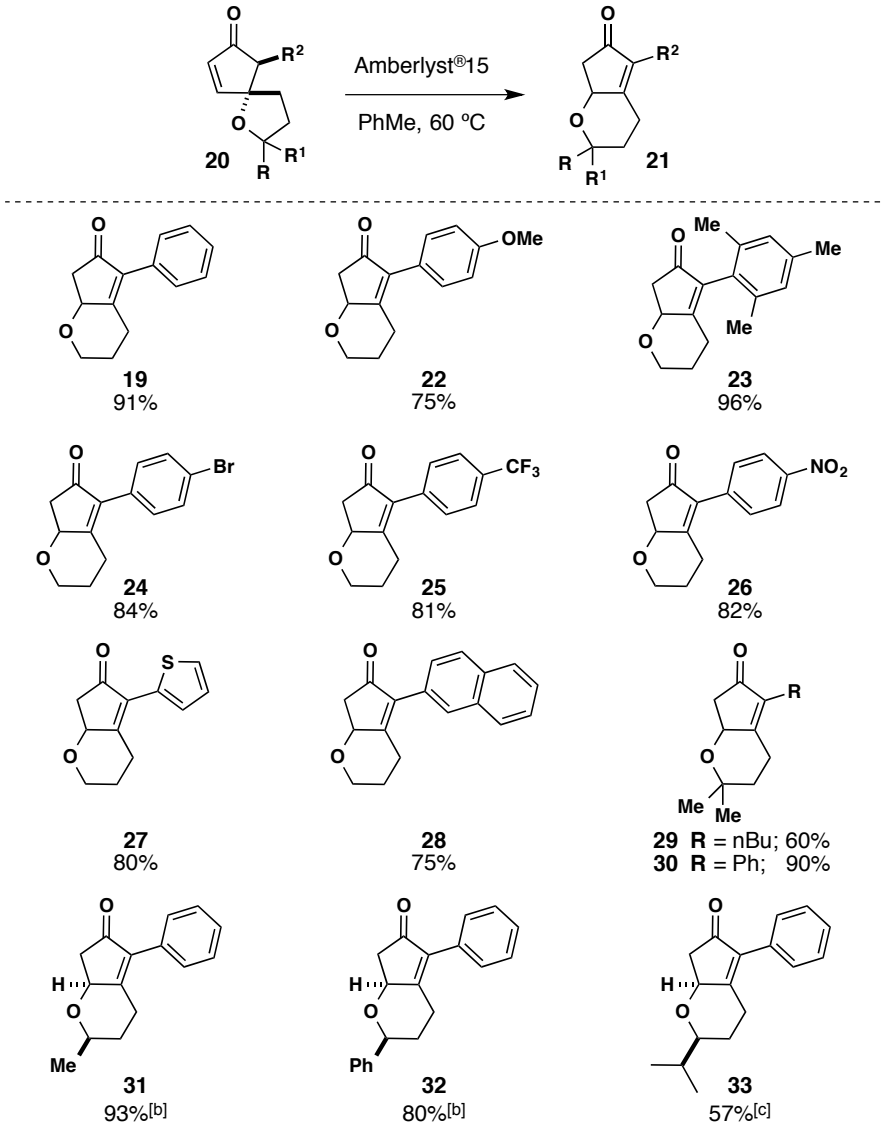
Entry	Reagent (mol %)[a]	Yield (%) *trans*-6/*cis*-6/19[b]
1	Basic alumina (na)[c]	45:45:0
2	$ZnCl_2$ (20)	89:5:0
3	HCl (20)	57:3:0
4	H_2SO_4	decomposition
5	CSA (20)	66:9:0
6	*p*-TSA (20)	41:3:36
7	PMA (20)	45:45:0
8	**Amberlyst® 15 (na)[c]**	**0:0:91**

[a] CSA= camphorsulfonic acid, *p*-TSA = *p*-toluenesulfonic acid, PMA =poly-phosphomolybdic acid. [b] Determined by analysis of the reaction mixture by ^{1}H NMR spectroscopy. [c] na = not applicable.

Importantly, this skeletal rearrangement is general and can be used to efficiently prepare the fused oxabicycles directly from their spirocyclic precursors in high yield (Table 8.2). All substrates subjected to the reaction conditions behaved accordingly. The rearrangement was extremely clean for electron rich, poor and bulky substituted cyclopentenones (**22**, **23**, **24**–**26**), but slower and slightly lower yielding when the ether oxygen was substituted with a *gem*-dimethyl group (**29** and **30**). We were thrilled to discover that treatment of a mixture of diastereomers at the γ position of the spirocyclic ether to the reaction conditions resulted in

the formation of a single diastereomer of the bicyclic ether (**31** and **32**). An *anti* relationship, corresponding to the more thermodynamically stable product, was confirmed by NOE experiments.

Table 8.2. Scope of the molecular rearrangement.[a]



[a] Yield of isolated product. [b] The product was isolated as a single diastereomer. [c] A 7:1 ratio of diastereomers was obtained.

Interestingly, for the isopropyl substrate **33**, only a 7:1 ratio was achieved. The molecular rearrangement allowed efficient access to chrycorin (**27**), a natural product with

plant growth inhibitor properties, isolated from *Chrysanthemum coranarium* by Tada and Chiba.[242,243,246] Moreover, the skeletal rearrangement demonstrated that spirocyclic ethers are a viable intermediate in the synthesis of oxabicyclic cyclopentenones from an acid catalyzed cascade rearrangement of α-furylcarbinols.

From a mechanistic and synthetic point of view, it is interesting that only a single diastereomer is isolated in the case of substituted products **31** and **32** from a 2:1 diastereomeric mixture of the starting materials. It could be considered that the skeletal rearrangement follows a stepwise pathway (Figure 8.3), that allows for the interconversion of intermediates to the thermodynamically favored cyclopentenone framework **19**. In acidic media, protonation of spirocylic ether **34** in combination with the acidity of the (here, benzylic) proton in **35** and the proximity of the carbonyl group leads to cleavage of the ether to give alcohol **36**. This extremely reactive species would close rapidly through attack of the primary alcohol to give intermediate **37**, which upon tautomerization yields the thermodynamically favored, fused cyclopentenone **19**.

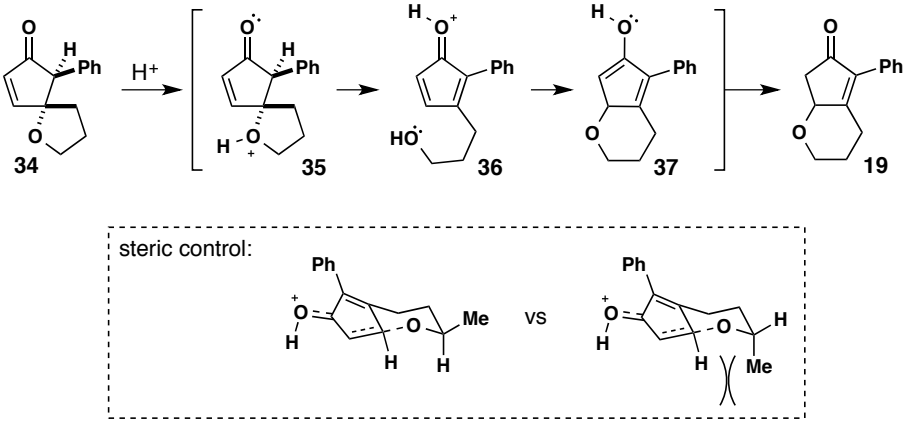


Figure 8.3. Possible mechanism of the skeletal rearrangement and proposed source of selectivity.

If a secondary alcohol is used, as in the case of products **31** to **32**, having the secondary alcohol-substituent in an equatorial position during ring closure minimizes unfavorable steric interactions (Figure 8.3). The possibility of introducing 1,3-diaxial interactions is illustrated clearly in the obtained crystal structure of product **31** (Figure 8.4).

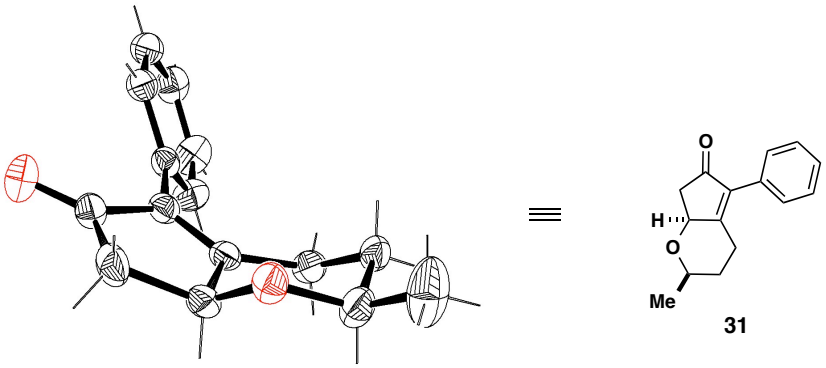
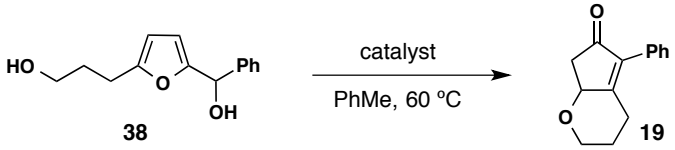


Figure 8.4. ORTEP drawing of oxabicycle **31**. Ellipsoids draws at 30% probability. CCDC 931233.

It is also noteworthy that we can access the desired fused cyclopentenone framework directly from furfural-derived starting materials (Table 8.3).[242,243] Treatment of furylcarbinol **38** with Amberlyst®15 and heating in toluene at 60 °C gave the desired product (**19**) in 39% yield (Table 8.3, entry 1). Heating the furylcarbinol at 100 °C followed by treatment with Amberlyst®15 at 60 °C produced the product in only 16% yield. We were surprised to discover that the treatment of furylcarbinol **38** with $Dy(OTf)_3$ and Amberlyst®15 concurrently (Table 8.3, entry 3) gave the fused cyclopentenone **19** in only 34% yield. Based on Wu's one-pot protocol where water was found to be critical for obtaining good yields, [242,243] we tested if water would have a similar effect on the one-pot reaction in Table 8.3. Unfortunately, the addition of water as a co-solvent (1:1, H_2O:PhMe) gave similar results. During the course of these reactions, spirocyclic ether **6** was observed, along with a number of byproducts. These results suggest that our one-pot reactions are going through the

formation of **6**, which is presumably low yielding. This is not entirely surprising because in previous studies for the formation of **6** from the corresponding furylcarbinol **38**, extensive optimization of the reaction conditions was required to achieve good yields.[139] Although our protocol allows for direct access to the fused cyclopentenone **19** directly from furylcarbinol **38**, the described two-step protocol is superior for the conversion of spirocycle **6** to cyclopentenone **19**.

Table 8.3. Testing a one-pot procedure.



Entry	Catalyst	Yield (%)
1	Amberlyst® 15	39
2	100 °C, then Amberlyst® 15	16
3	$Dy(OTf)_3$ (5 mol %) + Amberlyst® 15	34

In conclusion, we discovered an operationally simple conversion of spirocyclic ethers to fused bicyclic ethers through an acid catalyzed isomerization. This transformation provides direct access to fused oxabicycles, which are important intermediates in the total synthesis of numerous biologically active molecules. This approach to fused oxabicycles is attractive because it demonstrates the versatile nature of using renewable resources to build molecular diversity and as such, current efforts are focused on extending the methodology to include industrially important transformations and utilizing our products as substrates for further synthetic manipulations.

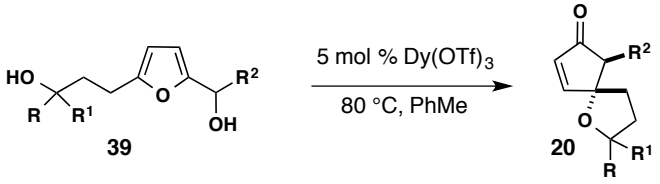
8.3. Experimental Procedures

Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially

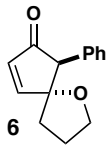
obtained reagents were used as received. Reaction temperatures were controlled using an Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 230-240 mesh, Merck KGA). ^{1}H NMR spectra were recorded on Varian spectrometers (at 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 or 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum Two FT/IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Santa Barbara Mass Spectrometry Facility on a (Waters Corp.) Micromass QTOF2 with an electrospray ionization source. X-ray data were obtained from the UC Santa Barbara X-ray Facility.

4,5-Substituted oxa-spirocycles **20** were prepared from readily available commercial starting materials and following procedures previously disclosed.[139] The crystal structure data for oxa-bicycle **31** can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 931233.

General Procedure for Accessing Substrates:

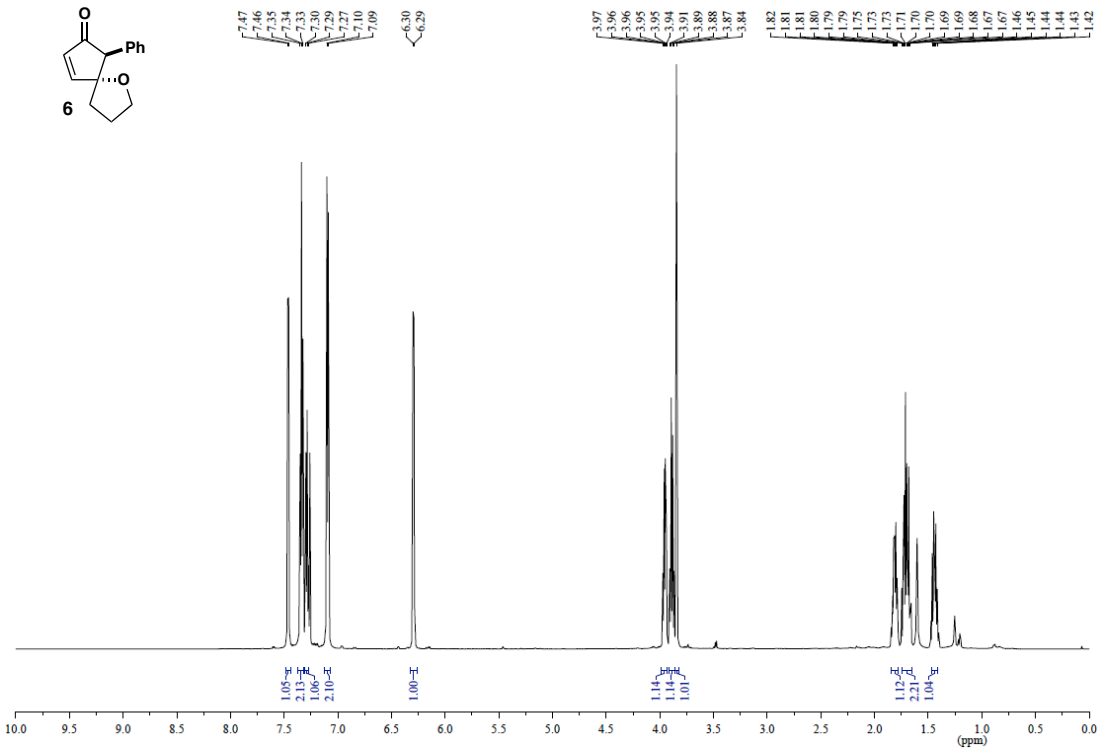


The Preparation of Oxaspirocycles: 5-Substituted furylcarbinols (**39**) were stirred as a solution in toluene at 23 ºC in base-washed glassware (KOH base bath, rinsed once with DI water and acetone) or a new scintillation vial. 5 mol % of $Dy(OTf)_3$ was added and the reaction flask immediately placed in an oil bath pre-heated to 80 ºC. The reaction was monitored by TLC. Upon completion, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by flash column chromatography to afford oxaspirocycles (**20**).



6

6-Phenyl-1-oxaspiro[4.4]non-8-en-7-one (6): Colorless, crystalline solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 5.8 Hz, 1H), 7.34 (dd, *J* = 7.5, 7.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.30 (d, *J* = 5.8 Hz, 1H), 3.96 (ddd, *J* = 7.8, 7.8, 5.4 Hz, 1H), 3.89 (dd, *J* = 15.0, 7.8 Hz, 1H), 3.84 (s, 1H), 1.81 (dddd, *J* = 12.2, 12.2, 6.8, 5.4 Hz, 1H), 1.72 (ddd, *J* = 13.0, 7.8, 7.8 Hz, 1H), 1.68 (ddd, *J* = 13.0, 7.8, 5.4 Hz, 1H), 1.44 (ddddd, *J* = 12.0, 7.7, 7.7, 7.7, 7.7 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.4, 163.9, 136.1, 132.9, 130.2, 128.8, 127.5, 91.1, 69.0, 63.7, 33.1, 26.2 ppm; **IR** (thin film) 3030, 2926, 1713, 1602, 1497, 1453, 1341, 1251, 1176, 1050 cm^{-1}; **MS** (ESI) *m/z* 237.09 (237.09 calcd for $C_{14}H_{14}NaO_2^+$ $[MNa]^+$).


O
Ph
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6
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7.46
7.35
7.34
7.33
7.30
7.29
7.27
7.10
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6.29
3.97
3.96
3.96
3.95
3.95
3.94
3.91
3.89
3.88
3.87
3.84
1.82
1.81
1.81
1.80
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1.73
1.73
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1.46
1.45
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1.44
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1.06
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1.14
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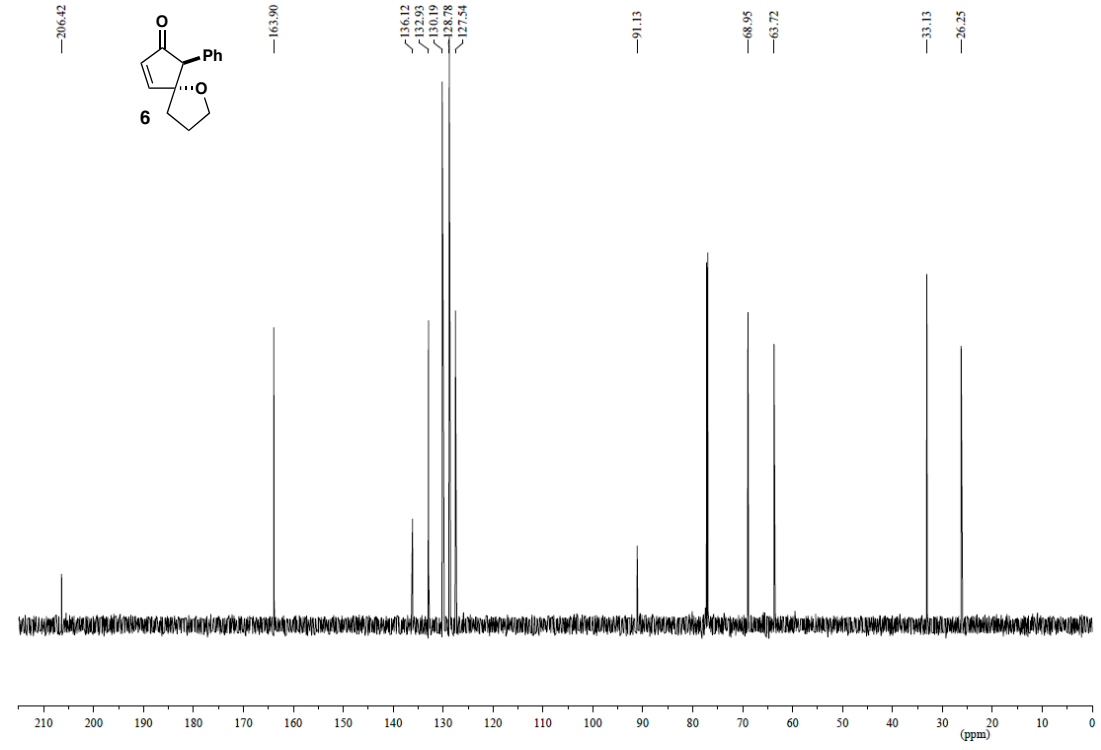
1.01
1.12
2.21
1.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
(ppm)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Ph
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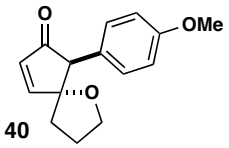
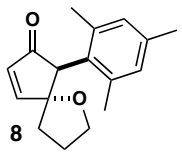
163.90
136.12
132.93
130.19
128.78
127.54
91.13
68.95
63.72
33.13
26.25
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)



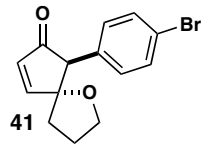
40

6-(4-Methoxyphenyl)-1-oxaspiro[4.4]non-8-en-7-one (40): Pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.0 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 6.28 (d, *J* = 6.0 Hz, 1H), 3.95 (ddd, *J* = 7.8, 7.8, 5.0 Hz, 1H), 3.88 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.80 (s, 4H), 1.82 (ddddd, *J* = 12.0, 6.6, 6.6, 6.6, 5.0 Hz, 1H), 1.73 – 1.68 (m, 2H), 1.45 (ddddd, *J* = 12.0, 7.8, 7.8, 7.8, 7.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.6, 163.8, 159.0, 132.9, 131.3, 128.0, 114.3, 91.1, 69.0, 63.1, 55.5, 33.2, 26.3 ppm; **IR** (thin film) 3079, 2924, 2874, 1717, 1593, 1437, 1341, 1216, 1121, 1051 cm^{-1}; **MS** (ESI) *m/z* 267.11 (267.10 calcd for $C_{15}H_{16}NaO_3^+$ $[MNa]^+$).

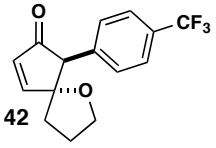


8

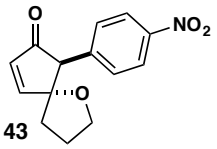
6-Mesityl-1-oxaspiro[4.4]non-8-en-7-one (8): Colorless, crystalline solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 5.7 Hz, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 6.25 (d, *J* = 5.7 Hz, 1H), 4.23 (s, 1H), 3.88 (ddd, *J* = 7.8, 7.8, 6.6 Hz, 1H), 3.86 (ddd, *J* = 15.0, 7.8, 5.4 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 1.93 (ddddd, *J* = 13.2, 6.6, 6.6, 6.6, 6.6 Hz, 1H), 1.89 (s, 3H), 1.84 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H), 1.73 (ddd, *J* = 13.2, 7.2, 7.2 Hz, 1H), 1.65 (ddddd, *J* = 12.6, 6.6, 6.6, 6.6, 6.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 207.0, 163.2, 139.4, 137.1, 137.0, 132.0, 130.5, 130.3, 129.4, 91.5, 68.2, 58.9, 31.2, 27.1, 22.4, 21.4, 21.1 ppm; IR (thin film) 2924, 2863, 1717, 1613, 1484, 1459, 1379, 1338, 1273, 1124, 1073, 1048 cm^{-1}; **MS** (ESI) *m/z* 279.14 (279.14 calcd for $C_{17}H_{20}NaO_2^+$ $[MNa]^+$).



6-(4-Bromophenyl)-1-oxaspiro[4.4]non-8-en-7-one (41): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 5.7 Hz, 1H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 5.7 Hz, 1H), 3.95 (ddd, *J* = 7.8, 7.8, 5.0 Hz, 1H), 3.89 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 3.82 (s, 1H), 1.84 (ddddd, *J* = 12.0, 6.6, 6.6, 6.6, 5.0 Hz, 1H), 1.74 (ddd, *J* = 13.0, 8.1, 8.1 Hz, 1H), 1.64 (ddd, *J* = 13.0, 7.8, 5.4 Hz, 1H), 1.45 (ddddd, *J* = 12.0, 7.8, 7.8, 7.8, 7.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.6, 163.9, 135.0, 132.8, 132.0, 131.9, 121.7, 90.9, 69.0, 63.1, 33.2, 26.3 ppm; **IR** (thin film) 3063, 2926, 2875, 1715, 1589, 1489, 1444, 1406, 1341, 1220, 1172, 1073, 1051, 1012 cm^{-1}; **MS** (ESI) *m/z* 315.01 (100%), 317.01 (100), 316.02 (21) (315.00, 317.00, 316.00 calcd for $C_{14}H_{13}BrNaO_2^+$ $[MNa]^+$).

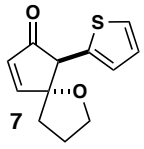


6-(4-(Trifluoromethyl)phenyl)-1-oxaspiro[4.4]non-8-en-7-one (42): Colorless, crystalline solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 5.7 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 6.31 (d, *J* = 5.7 Hz, 1H), 3.96 (ddd, *J* = 7.8, 7.8, 5.0 Hz, 1H), 3.93 (s, 1H), 3.90 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 1.85 (ddddd, *J* = 12.0, 6.7, 6.7, 6.7, 5.1 Hz, 1H), 1.76 (ddd, *J* = 13.0, 7.8, 7.8 Hz, 1H), 1.61 (ddd, *J* = 13.0, 7.8, 5.4 Hz, 1H), 1.43 (ddddd, *J* = 12.0, 7.8, 7.8, 7.8, 7.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.3, 164.0, 140.1, 132.7, 130.6, 124.3 (q, *J* = 270 Hz), 125.7 (q, *J* = 4 Hz), 129.9 (q, *J* = 33 Hz), 91.0, 69.0, 63.4, 33.2, 26.3 ppm; **IR** (thin film) 2928, 1717, 1620, 1420, 1327, 1165, 1124, 1112, 1068, 1020 cm^{-1}; **MS** (ESI) *m/z* 305.09 (305.08 calcd for $C_{15}H_{13}F_3NaO_2^+$ $[MNa]^+$).



43

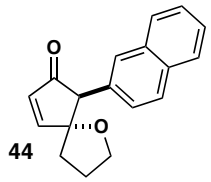
6-(4-Nitrophenyl)-1-oxaspiro[4.4]non-8-en-7-one (43): Pale solid and inseperable from the epimerized *cis* product in a 9:1 ratio. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 5.7 Hz, 1H), 7.31 (d, *J* = 8.7 Hz, 2H), 6.32 (d, *J* = 5.7 Hz, 1H), 4.00 (s, 1H), 3.98 (ddd, *J* = 7.8, 7.8, 5.4 Hz, 1H), 3.91 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 1.87 (ddddd, *J* = 12.0, 6.6, 6.6, 6.6, 5.4 Hz, 1H), 1.78 (ddd, *J* = 13.0, 7.8, 7.8 Hz, 1H), 1.58 (ddd, *J* = 13.0, 7.8, 5.4 Hz, 1H), 1.48 (ddddd, *J* = 12.0, 7.8, 7.8, 7.8, 7.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 204.4, 164.0, 143.6, 134.1, 132.6, 131.2, 124.0, 91.0, 69.1, 63.3, 33.2, 26.3 ppm; **IR** (thin film) 3080, 2924, 1715, 1604, 1519, 1346, 1174, 1110, 1053, 1020, cm^{-1}; **MS** (ESI) *m/z* 282.08 (282.07 calcd for $C_{14}H_{13}NNaO_4^+$ $[MNa]^+$).



7

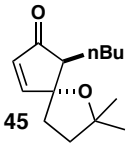
6-(Thiophen-2-yl)-1-oxaspiro[4.4]non-8-en-7-one (7): Pale orange solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.7 Hz, 1H), 7.28 (d, *J* = 4.8 Hz, 1H), 7.03 (dd, *J* = 4.8, 3.0 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.27 (d, *J* = 5.7 Hz, 1H), 4.16 (s, 1H), 4.03 (ddd, *J* = 7.6, 7.6, 4.8 Hz, 1H), 3.92 (ddd, *J* = 14.8, 7.6, 7.6 Hz, 1H), 1.91 – 1.85 (m, 1H), 1.83 (ddd, *J* = 13.0, 7.8, 5.4 Hz, 1H), 1.75 (ddd, *J* = 13.0, 7.8, 7.8 Hz, 1H), 1.61 (ddddd, *J* = 10.2, 7.8, 7.8, 7.8, 7.8 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.9, 163.3, 136.6, 132.1, 127.8, 127.2, 125.4, 90.9, 69.3, 58.8, 33.2, 26.5 ppm; **IR** (thin film) 2919, 2851, 1717, 1592, 1437,

1340, 1216, 1121, 1051, cm^{-1}; **MS** (ESI) *m/z* 243.05 (243.05 calcd for $C_{12}H_{12}NaO_2S^+$ $[MNa]^+$).



44

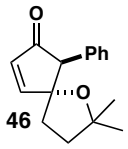
6-(Naphthalen-2-yl)-1-oxaspiro[4.4]non-8-en-7-one (44): Pale yellow solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 3H), 7.62 (s, 1H), 7.51 (d, *J* = 5.7 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.17 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.35 (d, *J* = 5.7 Hz, 1H), 4.03 (s, 1H), 3.98 (ddd, *J* = 7.8, 7.8, 4.8 Hz, 1H), 3.91 (ddd, *J* = 7.6, 7.6, 7.6 Hz, 1H), 1.79 (ddddd, *J* = 9.6, 7.2, 7.2, 7.2, 5.4 Hz, 1H), 1.78 – 1.70 (m, 2H), 1.44 (ddddd, *J* = 9.6, 7.6, 7.6, 7.6, 7.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.5, 164.0, 133.7, 133.6, 133.0, 132.8, 129.5, 128.5, 128.0, 127.8, 127.7, 126.4, 126.2, 91.2, 69.0, 63.8, 33.2, 26.4 ppm; **IR** (thin film) 3056, 2924, 1712, 1631, 1600, 1508, 1441, 1341, 1273, 1171, 1125, 1049 cm^{-1}; **MS** (ESI) *m/z* 287.11 (287.10 calcd for $C_{18}H_{16}NaO_2^+$ $[MNa]^+$).



45

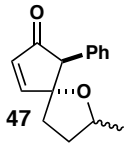
6-Butyl-2,2-dimethyl-1-oxaspiro[4.4]non-8-en-7-one (45): Yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.35 (d, *J* = 5.7 Hz, 1H), 6.04 (d, *J* = 5.7 Hz, 1H), 2.45 (t, *J* = 6.3 Hz, 1H), 2.17 (ddd, *J* = 7.2, 7.2, 5.4 Hz, 1H), 1.99 – 1.86 (m, 3H), 1.73 – 1.67 (m, 1H), 1.62 – 1.55 (m, 1H), 1.49 – 1.42 (m, 2H), 1.39 – 1.33 (m, 2H), 1.34 (s, 3H), 1.30 (s, 3H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 208.2, 164.7, 131.2, 90.5, 81.9, 55.9, 39.1, 32.0, 30.3, 29.7, 29.3, 25.7, 23.1, 14.1 ppm; **IR** (thin film) 2963, 2932, 2873, 1717, 1459,

1367, 1263, 1133, 1026 cm^{-1}; **MS** (ESI) *m/z* 245.16 (245.15 calcd for $C_{14}H_{22}NaO_2^+$ $[MNa]^+$).



46

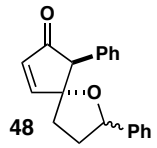
2,2-Dimethyl-6-phenyl-1-oxaspiro[4.4]non-8-en-7-one (46): Pale, crystalline solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.4 Hz, 1H), 7.35 (dd, *J* = 7.5, 7.2 Hz, 2H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.25 (d, *J* = 5.4 Hz, 1H), 3.82 (s, 1H), 1.87 (ddd, *J* = 13.2, 7.8, 7.8 Hz, 1H), 1.76 (ddd, *J* = 13.2, 6.6, 6.6 Hz, 1H), 1.66 (ddd, *J* = 13.0, 6.6, 6.6 Hz, 1H), 1.35 – 1.29 (m 1H), 1.30 (s, 3H), 1.24 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 206.4, 165.2, 135.9, 132.3, 130.4, 128.7, 127.5, 91.4, 82.7, 64.3, 38.4, 33.4, 29.1, 28.9 ppm; **IR** (thin film) 3063, 3031, 2971, 2931, 2873, 1717, 1594, 1498, 1454, 1382, 1368, 1339, 1259, 1135, 1034 cm^{-1}; **MS** (ESI) *m/z* 265.13 (265.12 calcd for $C_{16}H_{18}NaO_2^+$ $[MNa]^+$).



47

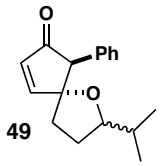
2-Methyl-6-phenyl-1-oxaspiro[4.4]non-8-en-7-one (47): Pale, crystalline solid, 2:1 mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.48 (d, *J* = 6.0 Hz, $1H_{(MAJ)}$), 7.48 (d, *J* = 6.0 Hz, $1H_{(min)}$), 7.36 – 7.28 (m, 3H), 7.12 (d, *J* = 7.8 Hz, $2H_{(MAJ)}$), 7.08 (d, *J* = 7.8 Hz, $2H_{(min)}$), 6.29 (d, *J* =6.0 Hz, $1H_{(min)}$), 6.27 (d, *J* =6.0 Hz, $1H_{(MAJ)}$), 4.23 – 4.12 (m, 1H), 3.85 (s, $3H_{(MAJ)}$), 3.84 (s, $3H_{(min)}$), 1.82 – 1.65 (m, 3H), 1.52 - 1.46 (m, $1H_{(min)}$) 1.26 (d, *J* = 6.6 Hz, $3H_{(min)}$), 1.25 (d, *J* = 6.6 Hz, $3H_{(MAJ)}$), 0.97 – 0.91 (m, $1H_{(MAJ)}$) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ [MAJOR]: 206.1, 164.3, 135.4, 132.4, 130.4, 128.7, 127.6, 91.1, 76.4, 64.2,

33.7, 33.6, 21.2, [minor]: 206.7, 164.9, 136.7, 132.8, 130.1, 128.9, 127.5, 91.3, 76.8, 64.0, 33.6, 33.2, 22.2 ppm; **IR** (thin film) 3031, 2971, 2929, 1715, 1601, 1498, 1453, 1382, 1340, 1314, 1227, 1172, 1139, 1108, 1078, 1012 cm^{-1}; **MS** (ESI) *m/z* 251.11 (251.10 calcd for $C_{15}H_{16}NaO_2^+$ $[MNa]^+$).



48

2,6-Diphenyl-1-oxaspiro[4.4]non-8-en-7-one (48): Pale oil, 2:1 mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, *J* = 6.0 Hz, $1H_{(MAJ)}$), 7.59 (d, *J* = 6.0 Hz, $1H_{(min)}$), 7.39 – 7.27 (m, 8H), 7.15 (d, *J* = 7.8 Hz, $2H_{(min)}$), 7.12 (d, *J* = 7.2 Hz, $2H_{(MAJ)}$), 6.35 (d, *J* = 6.0 Hz, $1H_{(min)}$), 6.34 (d, *J* = 6.0 Hz, $1H_{(MAJ)}$), 5.10 (t, *J* = 6.6 Hz, $1H_{(min)}$), 5.04 (dd, *J* = 9.3, 5.7 Hz, $1H_{(MAJ)}$), 4.03 (s, $1H_{(MAJ)}$), 4.01 (s, $1H_{(min)}$), 2.16 – 2.11 (m, $1H_{(MAJ)}$), 2.06 – 2.00 (m, $1H_{(min)}$), 1.96 – 1.79 (m, $2H_{(MAJ)}3H_{(min)}$) 1.43 – 1.36 (m, $1H_{(MAJ)}$) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ [MAJOR]: 206.2, 164.0, 141.5, 135.5, 132.9, 130.5, 128.8, 128.7, 127.9, 127.7, 126.0, 91.5, 81.5, 63.8, 34.7, 33.5 [minor]: 206.5, 164.0, 142.7, 136.6, 133.1, 130.2, 129.0, 128.7, 127.7, 125.6, 91.9, 82.0, 63.9, 35.0, 33.4 ppm; **IR** (thin film) 3062, 3031, 2926, 1714, 1602, 1497, 1452, 1342, 1267, 1217, 1158, 1078, 1043 cm^{-1}; **MS** (ESI) *m/z* 313.14 (313.12 calcd for $C_{20}H_{18}NaO_2^+$ $[MNa]^+$).

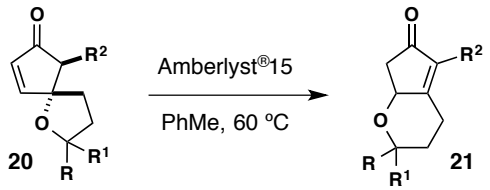


49

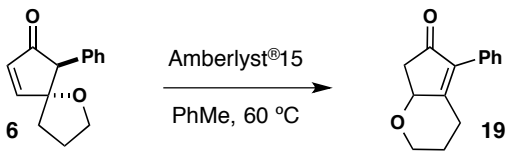
2-*iso*Propyl-6-phenyl-1-oxaspiro[4.4]non-8-en-7-one (49): Yellow oil, 2:1 mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 5.7 Hz, $1H_{(MAJ)}$), 7.42 (d, *J* = 5.7

Hz, $1H_{(min)}$), 7.35 – 7.27 (m, 3H), 7.09 (d, J = 7.2 Hz, 2H), 6.28 (d, J = 5.7 Hz, $1H_{(min)}$), 6.27 (d, J = 5.7 Hz, $1H_{(MAJ)}$), 3.86 (s, $1H_{(min)}$), 3.84 (s, $1H_{(MAJ)}$), 3.76 (ddd, J = 7.0, 7.0, 7.0 Hz, $1H_{(min)}$), 3.68 (ddd, J = 7.8, 7.8, 5.0 Hz, $1H_{(MAJ)}$), 1.76 – 1.50 (m, 4H), 1.10 – 1.02 (m, 1H), 1.00 (d, J = 6.6 Hz, $3H_{(MAJ)}$), 0.96 (d, J = 6.6 Hz, $3H_{(min)}$), 0.86 (d, J = 6.6 Hz, $3H_{(min)}$), 0.84 (d, J = 6.6 Hz, $3H_{(MAJ)}$) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ [MAJOR]: 206.5, 164.5, 135.7, 132.5, 130.4, 128.7, 127.5, 90.9, 85.8, 64.0, 33.4, 33.3, 29.4, 19.8, 18.7 [minor]: 206.9, 164.7, 136.9, 132.8, 130.1, 128.8, 127.5, 91.1, 86.2, 64.0, 33.5, 33.3, 29.0, 19.3, 18.4 ppm; **IR** (thin film) 3031, 2960, 2873, 1717, 1594, 1498, 1454, 1388, 1339, 1224, 1164, 1078, 1047 cm^{-1}; **MS** (ESI) *m/z* 279.15 (279.14 calcd for $C_{17}H_{20}NaO_2^+$ $[MNa]^+$).

Experimental Procedures

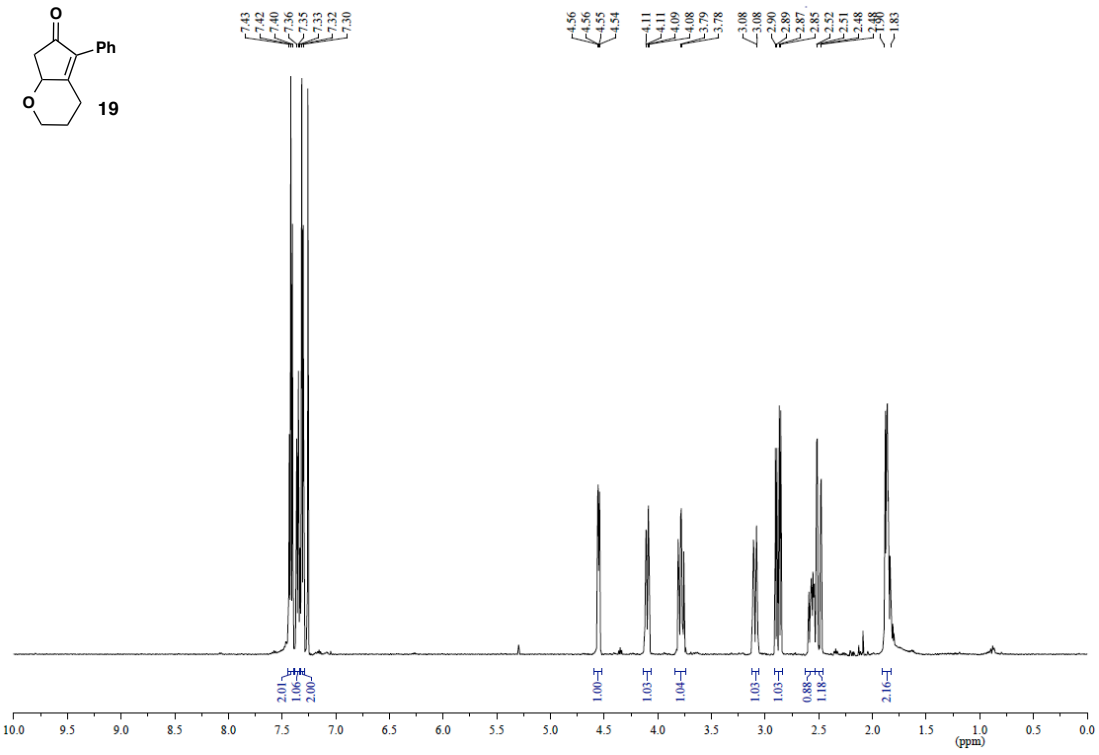


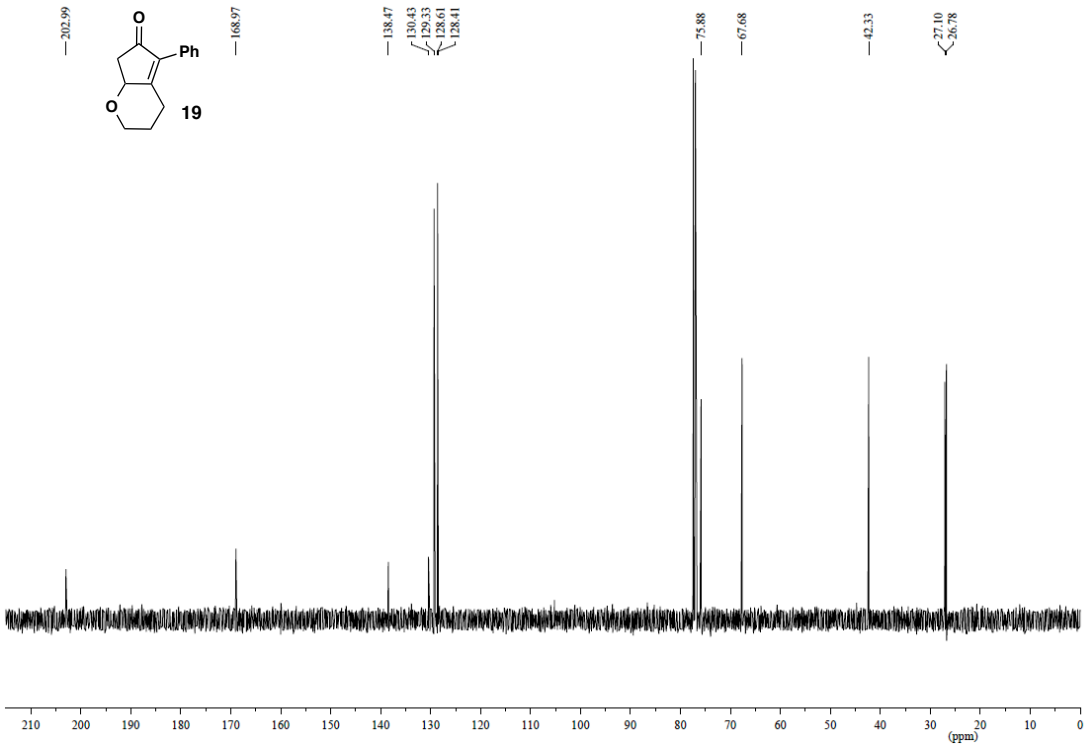
General Procedure for the Rearrangement of Spirocycles to Bicycles: Oxaspirocycles (**20**) were stirred as a solution in toluene at 23 ºC and treated with Amberlyst®15 (20 mg). The reaction flask was immediately placed in an oil bath pre-heated to 60 ºC. The reaction was monitored by TLC. Upon completion, the reaction was cooled to room temperature and filtered through cotton, eluted with ethyl acetate. The combined organic layers were concentrated *in vacuo* to afford oxabicycles (**21**).

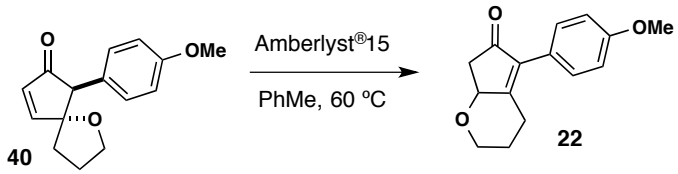


5-Phenyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (19): According to the general procedure Amberlyst®15 (20 mg) was added to 6-phenyl-1-oxaspiro[4.4]non-8-en-7-one **6** (10 mg, 0.047 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture

was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **19** (9.1 mg, 91%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (t, *J* = 8.9 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.31 (d, *J* = 10.0 Hz, 2H), 4.55 (dd, *J* = 7.8, 2.8 Hz, 1H), 4.12 – 4.17 (m, 1H), 3.81 – 3.76 (m, 1H), 3.13 – 3.06 (m, 1H), 2.88 (dd, *J* = 22.0, 7.8 Hz, 1H), 2.60 – 2.52 (m, 1H), 2.54 (dd, *J* = 22.0, 2.8 Hz, 1H), 1.90 – 1.83 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.0, 169.0, 138.5, 130.4, 129.3, 128.6, 128.4, 75.9, 67.7, 42.3, 27.1, 26.8 ppm; **IR** (thin film) 3398, 3058, 2956, 2925, 2850, 1706, 1647, 1496, 1445, 1326, 1295, 1137, 1090, 1049 cm^{-1}; **MS** (ESI) *m/z* 237.09 (237.09 calcd for $C_{14}H_{14}NaO_2^+$ $[MNa]^+$). Data was consistent with those found in the literature.[243]

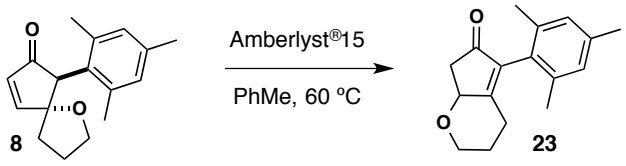




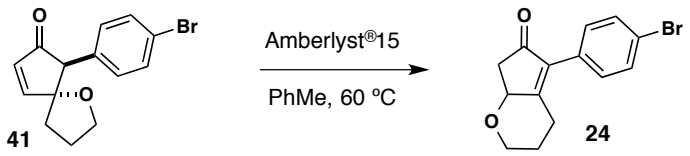


5-(4-Methoxyphenyl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (22): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(4-methoxyphenyl)-1-oxaspiro[4.4]non-8-en-7-one **40** (7.6 mg, 0.031 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **22** (5.7 mg, 75%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.53 (dd, *J* = 6.5, 2.2 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.83 (s, 3H), 3.78 (td, *J* = 11.0, 4.2 Hz, 1H), 3.12 – 3.07 (m, 1H), 2.86 (dd, *J* = 18.3, 6.5 Hz, 1H), 2.55 (dt, *J* = 14.3, 8.8 Hz,

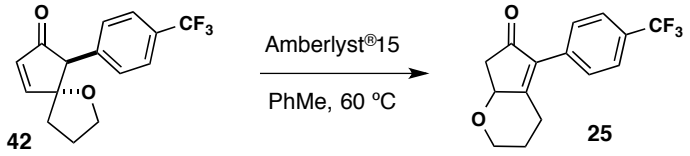
1H), 2.48 (dd, *J* = 18.3, 2.2 Hz, 1H), 1.88 – 1.82 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.3, 167.8, 159.7, 138.0, 130.6, 122.7, 114.1, 75.8, 67.7, 55.5, 42.3, 27.0, 26.8 ppm; **IR** (thin film) 3470, 2956, 2925, 2851, 1705, 1608, 1513, 1327, 1289, 1250, 1175, 1090, 1032 cm^{-1}; **MS** (ESI) *m/z* 267.11 (267.10 calcd for $C_{15}H_{16}NaO_3^+$ $[MNa]^+$). Data was consistent with those found in the literature.[243]



5-Mesityl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (23): According to the general procedure Amberlyst®15 (20 mg) was added to 6-mesityl-1-oxaspiro[4.4]non-8-en-7-one **8** (7.0 mg, 0.027 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **23** (7.0 mg, 98%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.88 (s, 1H), 4.59 (dd, *J* = 6.4, 2.3 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.78 – 3.73 (m, 1H), 2.88 (dd, *J* = 18.4, 6.4 Hz, 1H), 2.56 – 2.51 (m, 1H), 2.52 (dd, *J* = 18.4, 2.3 Hz, 1H), 2.37 – 2.30 (m, 1H), 2.28 (s, 3H), 2.08 (s, 3H), 1.99 (s, 3H), 1.88 – 1.82 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.3, 170.6, 139.3, 138.0, 136.7, 136.5, 128.5, 128.4, 126.9, 76.1, 67.7, 42.3, 27.1, 26.7, 21.3, 20.3, 20.1 ppm; **IR** (thin film) 3407, 2923, 2852, 1711, 1654, 1612, 1443, 1376, 1324, 1289, 1161, 1121, 1088, 1049, 1035 cm^{-1}; **MS** (ESI) *m/z* 279.14 (279.14 calcd for $C_{17}H_{20}NaO_2^+$ $[MNa]^+$).

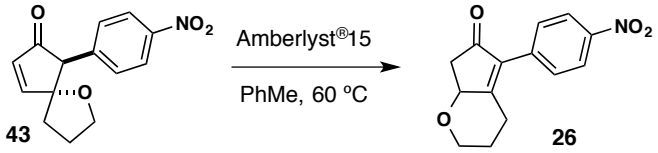


5-(4-Bromophenyl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (24): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(4-bromophenyl)-1-oxaspiro[4.4]non-8-en-7-one **41** (25 mg, 0.085 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **24** (21 mg, 84%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.19 (d, *J* = 8.4 Hz, 2H), 4.53 (dd, *J* = 6.5, 2.5 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.78 (td, *J* = 11.8, 3.0 Hz, 1H), 3.06 – 3.01 (m, 1H), 2.87 (dd, *J* = 18.4, 6.5 Hz, 1H), 2.55 (td, *J* = 13.5, 6.6 Hz, 1H), 2.48 (dd, *J* = 18.4, 2.5 Hz, 1H), 1.91 – 1.81 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 202.6, 169.4, 137.4, 131.8, 130.9, 129.3, 122.7, 75.8, 67.6, 42.2, 27.0, 26.8 ppm; **IR** (thin film) 3397, 2956, 2925, 2851, 1708, 1648, 1588, 1489, 1462, 1441, 1398, 1364, 1326, 1304, 1292, 1264, 1176, 1138, 1089, 1073, 1050, 1012 cm^{-1}; **MS** (ESI) *m/z* 315.01 (100%), 317.01 (100), 316.01 (17), 318.01 (17), (315.00, 317.00, 316.00, 318.00 calcd for $C_{14}H_{13}BrNaO_2^+$ $[MNa]^+$).



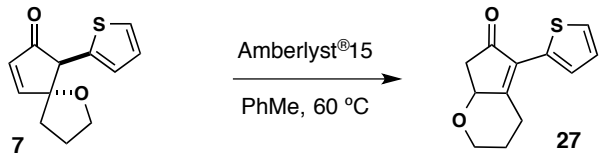
5-(4-(Trifluoromethyl)phenyl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (25): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(4-(trifluoromethyl)phenyl)-1-oxaspiro[4.4]non-8-en-7-one **42** (10 mg, 0.035 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to

room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **25** (8.1 mg, 81%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H), 4.62 (dd, *J* = 6.5, 2.4 Hz, 1H), 4.13 – 4.19 (m, 1H), 3.79 (td, *J* = 11.9, 2.6 Hz, 1H), 3.08 – 3.03 (m, 1H), 2.90 (dd, *J* = 18.5, 6.5 Hz, 1H), 2.60 (td, *J* = 13.5, 6.5 Hz, 1H), 2.52 (dd, *J* = 18.5, 2.4 Hz, 1H), 1.94 – 1.83 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 202.4, 170.4, 137.4, 134.1, 130.4 (q, *J* = 31 Hz), 129.7, 127.6 (q, *J* = 271 Hz), 126.1 (q, *J* = 4 Hz), 75.9, 67.6, 42.3, 27.1, 26.8 ppm; **IR** (thin film) 3406, 2958, 2927, 2852, 1709, 1650, 1616, 1411, 1365, 1327, 1299, 1166, 1125, 1091, 1067, 1050, 1020 cm^{-1}; **MS** (ESI) *m/z* 305.09 (305.08 calcd for $C_{15}H_{13}F_3NaO_2^+$ $[MNa]^+$).

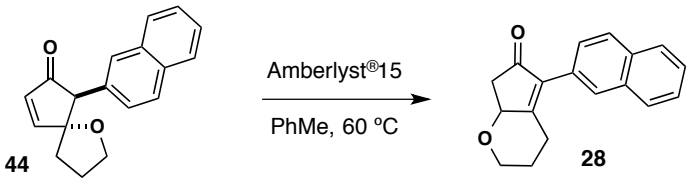


5-(4-Nitrophenyl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (26): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(4-nitrophenyl)-1-oxaspiro[4.4]non-8-en-7-one **43** (8.5 mg, 0.033 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **26** (7 mg, 82%) as a pale orange oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 4.58 (dd, *J* = 6.5, 2.3 Hz, 1H), 4.14 – 4.10 (m, 1H), 3.80 (td, *J* = 12.0, 2.3 Hz, 1H), 3.07 – 3.03 (m, 1H), 2.92 (dd, *J* = 18.5, 6.5 Hz, 1H), 2.63 (td, *J* = 13.6, 6.3 Hz, 1H), 2.53 (dd, *J* = 18.5, 2.3 Hz, 1H), 1.96 – 1.84 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 201.9, 171.4, 147.7, 137.2, 136.7, 130.3, 123.8, 75.9, 67.6, 42.3, 27.1, 27.0 ppm; **IR** (thin film) 3405, 2925, 2852, 1709, 1599, 1519,

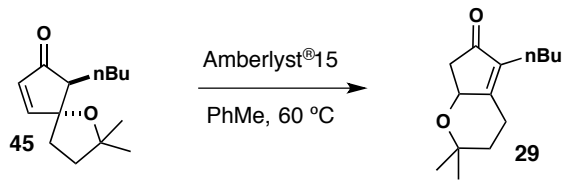
1347, 1326, 1300, 1138, 1090, 1049 cm^{-1}; **MS** (ESI) *m/z* 282.08 (282.07 calcd for $C_{14}H_{13}NNaO_4^+$ $[MNa]^+$). Data was consistent with those found in the literature.[243]



5-(Thiophen-2-yl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (27): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(thiophen-2-yl)-1-oxaspiro[4.4]non-8-en-7-one **7** (12.6 mg, 0.057 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **27** (10 mg, 80%) as a yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 3.7 Hz, 1H), 7.41 (d, *J* = 5.1 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.7 Hz, 1H), 4.53 (dd, *J* = 6.5, 2.7 Hz, 1H), 4.12 – 4.08 (m, 1H), 3.79 (td, *J* = 11.5, 3.5 Hz, 1H), 3.48 – 3.43 (m, 1H), 2.88 (dd, *J* = 18.4, 6.5 Hz, 1H), 2.62 (dt, *J* = 14.8, 10.0 Hz, 1H), 2.49 (dd, *J* = 18.4, 2.7 Hz, 1H), 1.94 – 1.89 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 201.8, 166.6, 131.4, 128.2, 127.3, 126.9, 120.7, 75.7, 67.6, 42.0, 27.1, 26.7 ppm; IR (thin film) 3102, 2923, 2851, 1702, 1630, 1428, 1323, 1292, 1219, 1162, 1122, 1090, 1048 cm^{-1}; **MS** (ESI) *m/z* 243.05 (243.05 calcd for $C_{12}H_{12}NaO_2S^+$ $[MNa]^+$). Data was consistent with those found in the literature.[243]

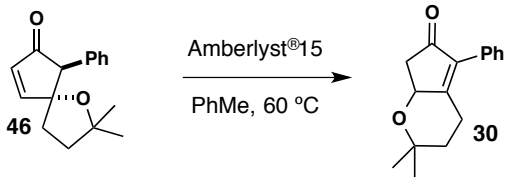


5-(Naphthalen-2-yl)-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (28): According to the general procedure Amberlyst®15 (20 mg) was added to 6-(naphthalen-2-yl)-1-oxaspiro[4.4]non-8-en-7-one **44** (10 mg, 0.038 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **28** (7.5 mg, 75%) as a pale yellow oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.5 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.81 (s, 1H), 7.51 – 7.48 (m, 2H), 7.42 (dd, *J* = 8.4, 1.5 Hz, 1H), 4.66 (dd, *J* = 6.5, 2.5 Hz, 1H), 4.14 – 4.10 (m, 1H), 3.84 – 3.79 (m, 1H), 3.18 – 3.13 (m, 1H), 2.93 (dd, *J* = 18.3, 6.5 Hz, 1H), 2.63 (dt, *J* = 14.5, 9.8 Hz, 1H), 2.55 (dd, *J* = 18.3, 2.5 Hz, 1H), 1.91 – 1.85 (m, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.1, 169.3, 138.5, 133.4, 133.2, 128.8, 128.4, 128.2, 127.9, 127.9, 126.8, 126.6, 126.4, 75.9, 67.7, 42.4, 27.1, 26.9 ppm; **IR** (thin film) 3398, 3057, 2957, 2925, 2852, 1708, 1646, 1596, 1506, 1461, 1441, 1374, 1323, 1310, 1294, 1271, 1261, 1139, 1118, 1090, 1049 cm^{-1}; **MS** (ESI) *m/z* 287.11 (287.10 calcd for $C_{18}H_{16}NaO_2^+$ $[MNa]^+$).

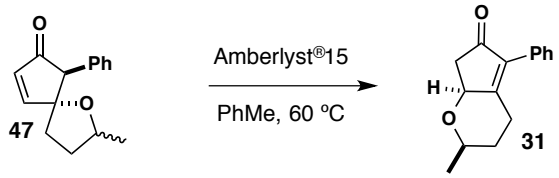


5-Butyl-2,2-dimethyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (29): According to the general procedure Amberlyst®15 (20 mg) was added to 6-butyl-2,2-dimethyl-1-oxaspiro[4.4]non-8-en-7-one **45** (9.0 mg, 0.045 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **29** (6.0 mg, 60%) as a very pale oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.64 (dd, *J* = 6.2, 2.4 Hz, 1H), 2.77 – 2.72 (m, 1H),

2.67 (dd, *J* = 18.1, 6.2 Hz, 1H), 2.53 (td, *J* = 14.0, 5.5 Hz, 1H), 2.26 (dd, *J* = 18.1, 2.4 Hz, 1H), 2.16 (t, *J* = 7.6 Hz, 2H), 1.80 (ddd, *J* = 13.3, 5.7, 2.4 Hz, 1H), 1.63 (td, *J* = 13.3, 4.8 Hz, 1H), 1.41 – 1.40 (m, 2H), 1.39 – 1.34 (m 1H), 1.31 – 1.28 (m, 1H), 1.25 (s, 6H), 0.89 (t, *J* = 7.3 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 205.3, 168.4, 139.1, 120.7, 72.9, 69.7, 42.6, 36.9, 31.0, 23.0, 22.8, 22.4, 21.9, 14.1 ppm; **IR** (thin film) 3410, 2958, 2928, 2857, 1710, 1659, 1465, 1366, 1288, 1125, 1075, 1029 cm^{-1}; **MS** (ESI) *m/z* 245.16 (245.15 calcd for $C_{14}H_{22}NaO_2^+$ $[MNa]^+$).

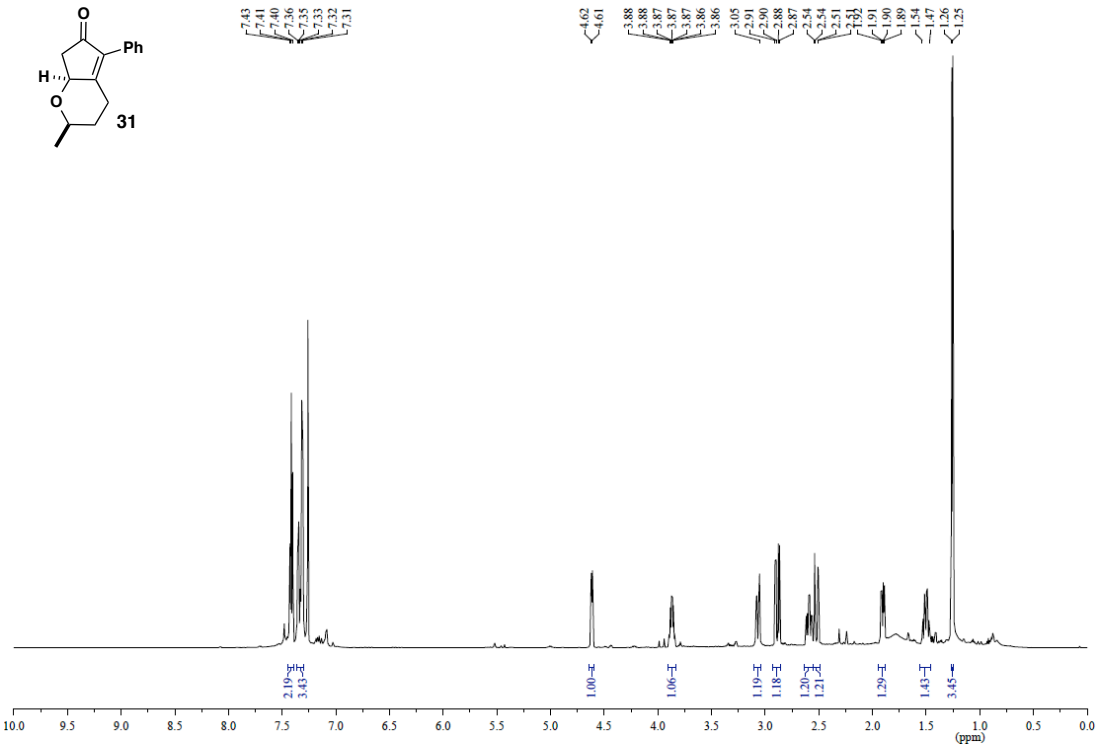


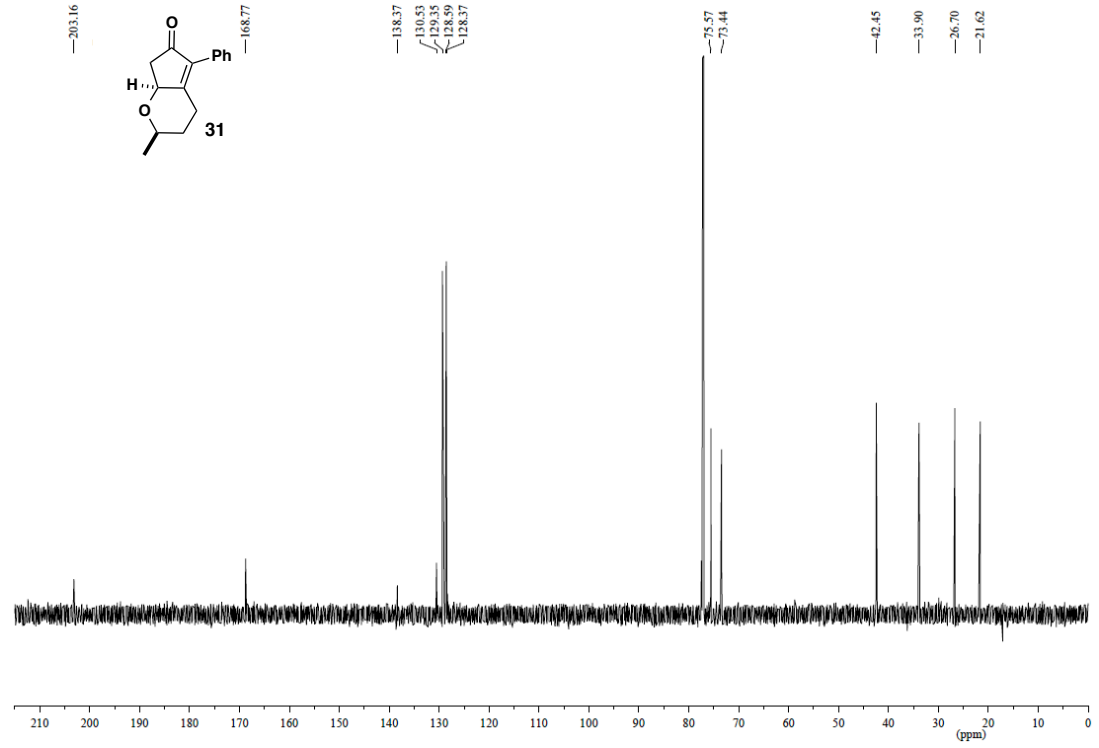
2,2-Dimethyl-5-phenyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (30): According to the general procedure Amberlyst®15 (20 mg) was added to 2,2-dimethyl-6-phenyl-1-oxaspiro[4.4]non-8-en-7-one **46** (10 mg, 0.041 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* and the residue purified by flash column chromatography to afford oxabicycle **30** (9 mg, 90%) as a colorless oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.6 Hz, 2H), 7.36 – 7.32 (m, 3H), 4.82 (dd, *J* = 6.4, 2.6 Hz, 1H), 2.97 – 2.93 (m, 1H), 2.86 (dd, *J* = 18.2, 6.4 Hz, 1H), 2.73 (td, *J* = 14.1, 5.9 Hz, 1H), 2.49 (dd, *J* = 18.2, 2.6 Hz, 1H), 1.78 (ddd, *J* = 13.4, 5.9, 2.2 Hz, 1H), 1.68 (td, *J* = 13.3, 4.9 Hz, 1H), 1.47 (s, 3H), 1.28 (s, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.2, 169.6, 130.6, 129.4, 128.6, 128.4, 120.7, 73.0, 69.6, 43.2, 36.8, 30.9, 23.8, 21.9 ppm; **IR** (thin film) 3401, 2924, 2852, 1706, 1627, 1446, 1363, 1328, 1298, 1262, 1145, 1116, 1077, 1043, 1019 cm^{-1}; **MS** (ESI) *m/z* 265.13 (265.12 calcd for $C_{16}H_{18}NaO_2^+$ $[MNa]^+$).

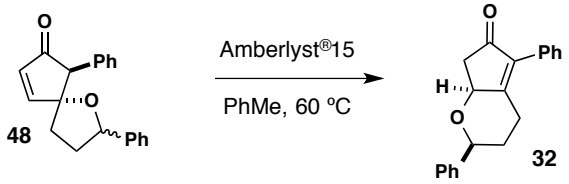


2-Methyl-5-phenyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (31):

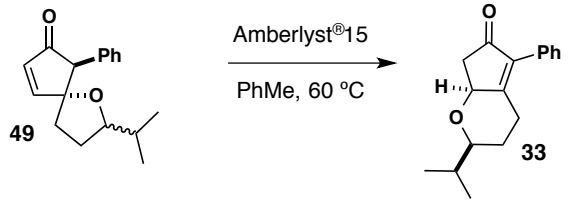
According to the general procedure Amberlyst®15 (20 mg) was added to 2-methyl-6-phenyl-1-oxaspiro[4.4]non-8-en-7-one **47** (10 mg, 0.044 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* to afford oxabicycle **31** (9.3 mg, 93%) as a colorless oil. Single diastereomer: relative stereochemistry determined by cycle nOe. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.62 (dd, *J* = 6.5, 2.5 Hz, 1H), 3.89 – 3.84 (m, 1H), 3.09 - 3.05 (m, 1H), 2.89 (dd, *J* = 18.3, 6.5 Hz, 1H), 2.59 (td, *J* = 13.9, 6.1 Hz, 1H), 2.52 (dd, *J* = 18.3, 2.5 Hz, 1H), 1.91 (ddt, *J* = 13.4, 6.1, 1.9 Hz, 1H), 1.50 (qd, *J* = 13.3, 4.7 Hz, 1H), 1.26 (d, *J* = 6.0 Hz, 3H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.2, 168.8, 138.4, 130.5, 129.4, 128.6, 128.4, 75.6, 73.4, 42.5, 33.9, 26.7, 21.6 ppm; **IR** (thin film) 3405, 2971, 2932, 2851, 1707, 1646, 1601, 1495, 1445, 1385, 1364, 1347, 1315, 1293, 1173, 1135, 1077, 1029 cm^{-1}; **MS** (ESI) *m/z* 251.11 (251.10 calcd for $C_{15}H_{16}NaO_2^+$ $[MNa]^+$).


O
Ph
H
O
31
7.43
7.41
7.40
7.36
7.35
7.33
7.32
7.31
4.62
4.61
3.88
3.88
3.87
3.87
3.87
3.87
3.86
3.86
3.05
2.91
2.90
2.88
2.87
2.54
2.54
2.51
2.51
1.92
1.91
1.90
1.89
1.54
1.47
1.26
1.25
2.19
3.43
1.00
1.06
1.19
1.18
1.20
1.21
1.29
1.43
3.45
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


O
Ph
H
O
31
203.16
168.77
138.37
130.53
129.35
128.59
128.37
75.57
73.44
42.45
33.90
26.70
21.62
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
(ppm)

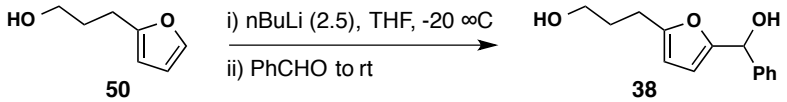


2,5-Diphenyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (32): According to the general procedure Amberlyst®15 (20 mg) was added to 2,6-diphenyl-1-oxaspiro[4.4]non-8-en-7-one **48** (10 mg, 0.034 mmol, 1 equiv) in toluene (1.2 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (10 mL). The combined organic layers were concentrated *in vacuo* and the residue purified by flash column chromatography to afford oxabicycle **32** (7.4 mg, 74%) as a yellow oil. Single diastereomer. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.40 – 7.35 (m, 6H), 7.32 – 7.22 (m, 2H), 4.82 (dd, *J* = 6.5, 2.6 Hz, 1H), 4.80 (dd, *J* = 11.7, 1.8, Hz, 1H), 3.20 (ddd, *J* = 14.6, 4.3, 1.6 Hz, 1H), 2.95 (dd, *J* = 18.4, 6.5 Hz, 1H), 2.78 (td, *J* = 13.9, 5.9 Hz, 1H), 2.66 (dd, *J* = 18.4, 2.6 Hz, 1H), 2.17 – 2.13 (m, 1H), 1.85 (qd, *J* = 13.2, 4.6 Hz, 1H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 203.1, 168.0, 141.4, 130.4, 129.4, 128.7 (2), 128.5, 128.1, 126.1, 120.7, 79.5, 76.2, 42.5, 34.3, 27.1 ppm; **IR** (thin film) 3398, 3061, 3031, 2923, 2851, 1706, 1646, 1601, 1496, 1447, 1312, 1294, 1134, 1078, 1044, 1002 cm^{-1}; **MS** (ESI) *m/z* 313.14 (313.12 calcd for $C_{20}H_{18}NaO_2^+$ $[MNa]^+$).



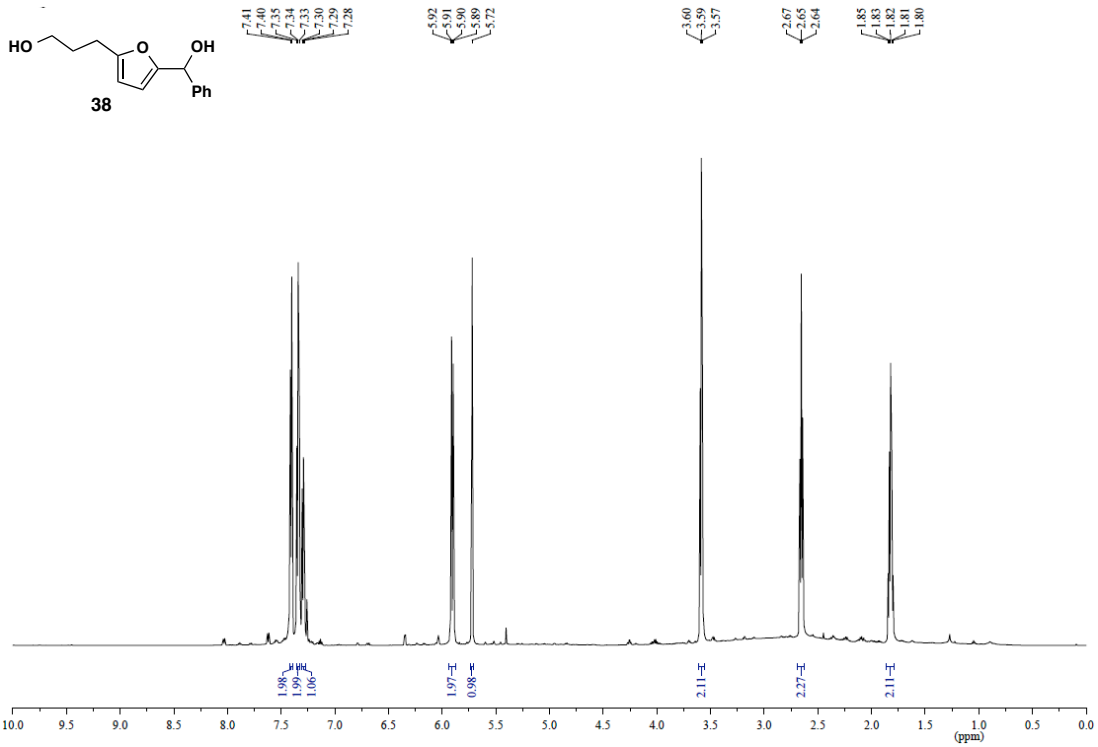
2-Isopropyl-5-phenyl-3,4,7,7a-tetrahydrocyclopenta[*b*]pyran-6(2*H*)-one (33): According to the general procedure Amberlyst®15 (20 mg) was added to 2-*iso*propyl-6-

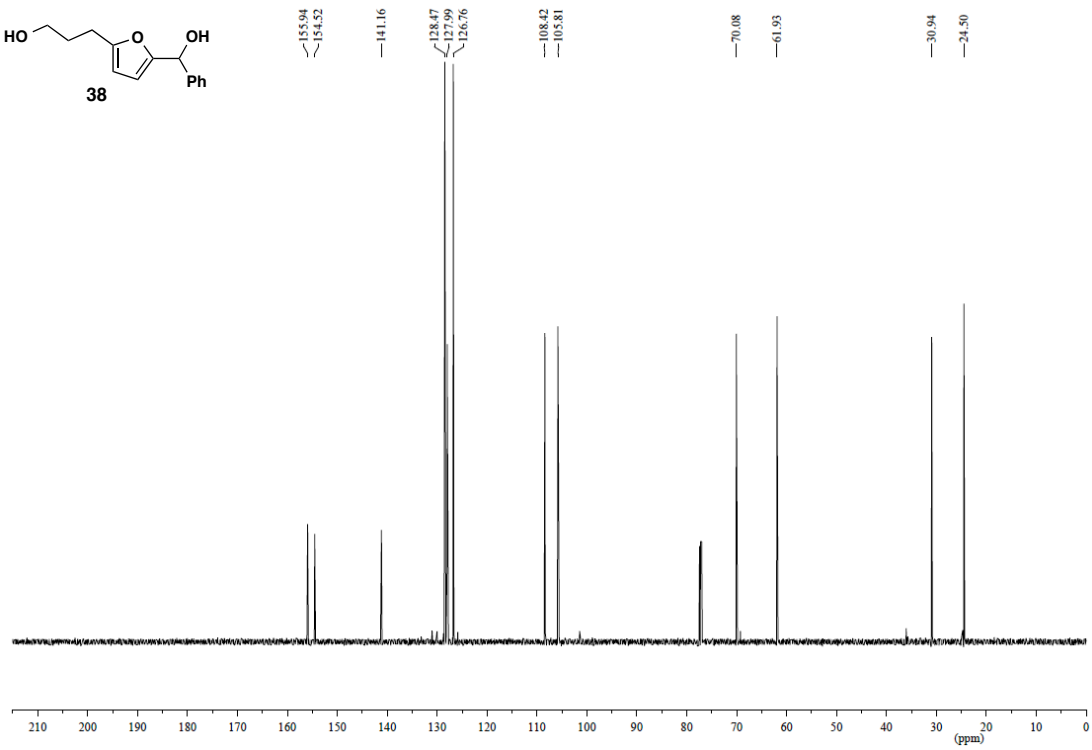
phenyl-1-oxaspiro[4.4]non-8-en-7-one **49** (30 mg, 0.117 mmol, 1 equiv) in toluene (3.6 mL). The resulting reaction mixture was heated to 60 ºC for 24 h then cooled to room temperature and filtered through cotton, eluted with ethyl acetate (15 mL). The combined organic layers were concentrated *in vacuo* and the residue purified by flash column chromatography to afford oxabicycle **33** (22 mg, 73%) as a colorless oil. 7:1 mixture of diastereomers. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 4.80 (dd, *J* = 6.5, 2.5 Hz, $1H_{(min)}$), 4.57 (dd, *J* = 6.5, 2.5 Hz, $1H_{(MAJ)}$), 3.49 – 3.46 (m, $1H_{(min)}$), 3.43 – 3.40 (m, $1H_{(MAJ)}$), 3.12 – 3.07 (m, 1H), 2.88 (dd, *J* = 18.3, 6.5 Hz, 1H), 2.55 (td, *J* = 13.8, 6.1 Hz, 1H), 2.52 (dd, *J* = 18.3, 2.5 Hz, $1H_{(MAJ)}$), 2.48 (dd, *J* = 18.3, 2.5 Hz, $1H_{(min)}$), 1.94 – 1.89 (m, 1H), 1.74 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.49 (qd, *J* = 13.0, 4.6 Hz, 1H), 1.08 (d, *J* = 6.5 Hz, $3H_{(min)}$), 0.98 (d, *J* = 6.9 Hz, $3H_{(MAJ)}$), 0.95 (d, *J* = 6.5 Hz, $3H_{(min)}$), 0.94 (d, *J* = 6.9 Hz, $3H_{(MAJ)}$) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ (MAJOR) 203.4, 169.6, 138.0, 130.6, 129.4, 128.6, 128.3, 82.3, 75.8, 42.5, 33.1, 28.9, 26.8, 18.8, 18.7 ppm; **IR** (thin film) 3405, 2959, 2922, 2851, 1709, 1464, 1446, 1324, 1292, 1166, 1136, 1078, 1053 cm^{-1}; **MS** (ESI) *m/z* 279.15 (279.14 calcd for $C_{17}H_{20}NaO_2^+$ $[MNa]^+$).



3-(5-(Hydroxy(phenyl)methyl)furan-2-yl)propan-1-ol (38): 2-Substituted furan **50** (519 mg, 4.12 mmol) was stirred as a solution in anh. THF (35 mL) at -20 ºC. *n*Butyllithium (3.93 mL, 10.3 mmol, 2.5 equiv.) was added dropwise and the reaction mixture stirred for 1 h at this temperature before the addition of benzaldehyde (1.05 mL, 10.3 mmol). The reaction flask was allowed to warm to room temperature over 2.5 h. The reaction was

quenched with saturated aqueous NH_4Cl (25 mL) and extracted with ethyl acetate (4 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered and then concentrated *in vacuo*. The residue was purified by column chromatography to afford 5-substituted furylcarbinol **38** (669 mg, 70%) as a pale crystalline solid; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.34 (dd, *J* = 7.6, 7.3 Hz, 2H), 7.29 (dd, *J* = 7.3, 7.3 Hz, 1H), 5.92 (d, *J* = 3.1 Hz, 1H), 5.90 (d, *J* = 3.1 Hz, 1H), 5.72 (s, 1H), 3.59 (t, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 7.5 Hz, 2H), 1.82 (dddd, *J* = 7.5, 7.5, 6.4, 6.4 Hz, 2H) ppm; **^{13}C NMR** (150 MHz, $CDCl_3$) δ 155.9, 154.5, 141.2, 128.5, 128.0, 126.8, 108.4, 105.8, 70.1, 61.9, 30.9, 24.5 ppm; **IR** (thin film) 3352(br), 2946, 2881, 1650, 1603, 1558, 1494, 1191, 1051, 1013, 966, 920 cm^{-1}; **MS** (ESI) *m/z* 255.10 (255.10 calcd for $C_{14}H_{16}NaO_3^+$ $[MNa]^+$).




HO
O
OH
Ph
38
155.94
154.52
141.16
128.47
127.99
126.76
108.42
105.81
70.08
61.93
30.94
24.50
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)

9. Miscellaneous Projects

9.1. Introduction

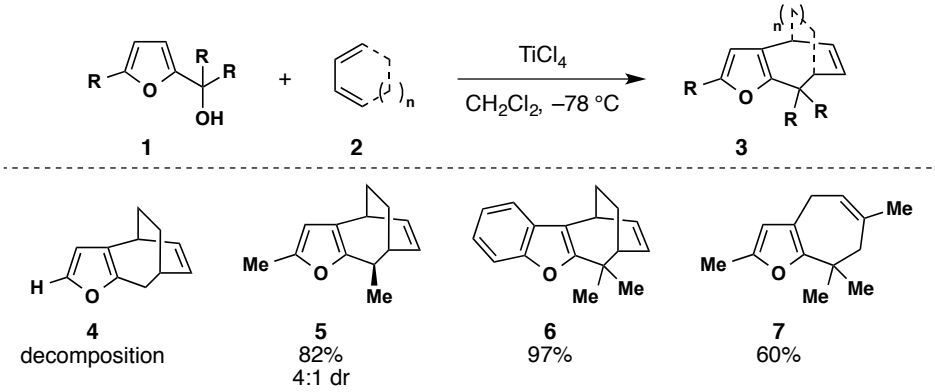
In this chapter, work and projects that could result in interesting new directions and research projects are discussed. Some of these areas were investigated out of curiosity during my Ph.D. studies, but never developed into complete projects.

9.2. Dysprosium Catalyzed [4+3] Cycloaddition

Our interest in cycloaddition reactions with furylcarbinols was sparked by a report by Johan Winne and co-workers in 2011. In their publication, the group described the development of a [4+3] cycloaddition of furylcarbinols **1** and dienes **2**,[247] inspired by the observation of an unexpected [4+3] cycloaddition during Pattenden and Winne's studies toward the total synthesis of rameswaralide.[248]

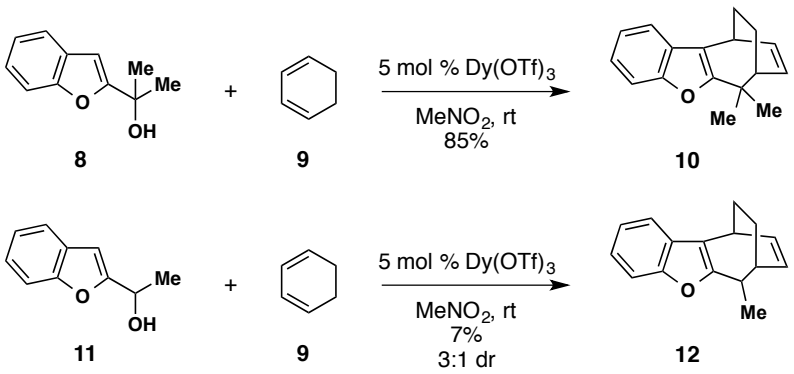
The cycloaddition worked well with a variety of furylcarbinols where the 5-position was blocked, and could be performed with a number of dienes. The reaction was facilitated by 1.5 equiv $TiCl_4$ at –78 °C in CH_2Cl_2 (Table 9.1). If the 5-position of furan was not blocked, the group observed polymerization/decomposition (**4**), and no formation of the desired product.

Table 9.1. Selected scope of Winne's [4+3] cycloaddition reaction.



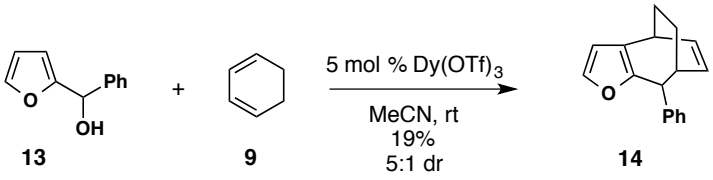
Because superstoichiometric amounts of a strong Lewis acid and cryogenic conditions were used, we wondered if dysprosium could serve as the catalyst in the [4+3] cycloaddition. We were confident that we could perform the reaction under milder conditions with much lower catalyst loadings based on our success with the dysprosium triflate catalyzed aza-Piancatelli rearrangement.[78] Additionally, we wondered if the mild nature of dysprosium might allow us to perform the reaction with furylcarbinols lacking the substituent at the 5-position.

To our delight, we found that 5 mol % $Dy(OTf)_3$ in $MeNO_2$ at rt effectively catalyzed the cycloaddition of furylcarbinol **8** and cyclohexadiene (**9)** to give **10** in 85% yield (Scheme 9.1). The reaction proceeded cleanly, and the yield is comparable to that achieved by Winne and co-workers (**6**, Table 9.1). Moreover, the experimental setup is extremely user friendly and requires no special skills or equipment. The reaction with furylcarbinol **11** gave **12** in only 7% yield with 3:1 dr. We presume that the secondary carbocation with only one methyl substituent is less stable and therefore may have resulted in increased decomposition.



Scheme 9.1. Dysprosium triflate catalyzed [4+3] cycloaddition of 5-substituted furylcarbinols and cyclohexadiene.

We chose to focus our attention on the reaction with furylcarbinols lacking a substituent at the 5-position. Pleasingly, reaction of phenyl furylcarbinol **13** with cyclohexadiene resulted in the formation of **14** in 19% yield in 5:1 dr using 5 mol % $Dy(OTf)_3$ in MeCN at rt (Scheme 9.2). Although the yield is quite low, this represents a huge improvement over the polymerization and decomposition observed by Winne and co-workers.



Scheme 9.2. Successful dysprosium catalyzed reaction.

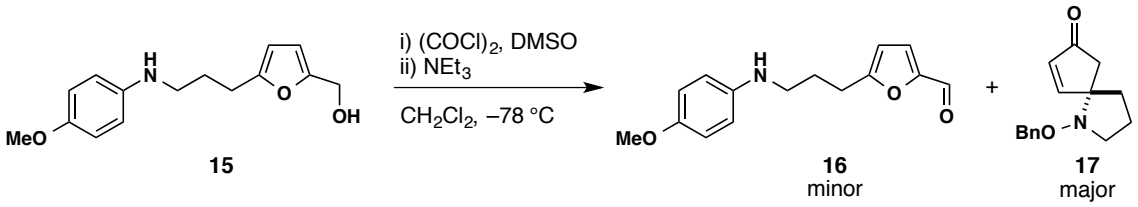
Unfortunately, subsequent studies showed no improvement in yield of the reaction. We screened all $RE(OTf)_3$ catalysts on hand (12), in addition to a number of solvents ($MeNO_2$, CH_2Cl_2, hexanes, Et_2O, THF, PhMe, EtOH, methyl *tert*-butyl ether) and different temperatures. We surmised that although activation does occur, decomposition of the furylcation occurs at a faster rate than cycloaddition. It may be possible to circumvent decomposition with a more reactive diene, but this has not yet been tested.

Despite the limited success in using $Dy(OTf)_3$ for the reaction with furylcarbinols lacking a substituent at the 5-position, the initial success reported opens up a novel area of research for our group. The reaction with benzofurans could be extended to other cycloaddition reactions, such as [3+2] cycloadditions,[249] and we could even envision departure from furan to other heterocycles, such as thiophene or indole. In fact, Wu and co-workers recently described a gallium(III)- catalyzed [4+3] cycloaddition reaction of dienes with indole.[250] Winne and co-workers subsequently utilized a gallium triflate catalyzed [4+3] cycloaddition in their efforts toward synthesizing the core ring system of guaianolides.[251]

Thinking about the potential of furylcations outside of the scope of the aza-Piancatelli rearrangement opens up a whole new area of research, and it is exciting to think about harnessing the potential of these carbocations using our mild dysprosium catalyzed conditions.

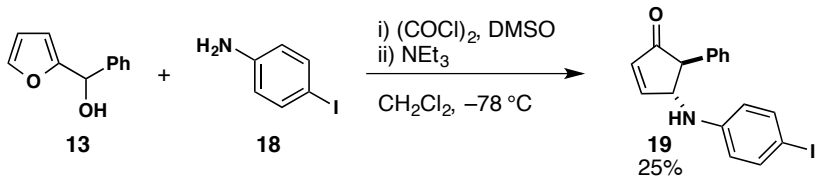
9.3. Alternative Activation of Furylcarbinols for the Aza-Piancatelli Rearrangement with Non-Aniline Amines

During the synthesis of some intramolecular aza-Piancatelli cyclization precursors, we discovered some interesting behavior under Swern oxidation conditions. During the planned synthesis of aldehyde **16** from furylcarbinol **15** via Swern oxidation, we observed only a small amount of the desired aldehyde, and found the main component of the reaction to be cyclopentenone **17** (Scheme 9.3), the product of an aza-Piancatelli rearrangement. This was quite a surprise to us, especially considering that synthesis of cyclopentenone **16** using our $Dy(OTf)_3$ catalyzed conditions had been quite challenging.



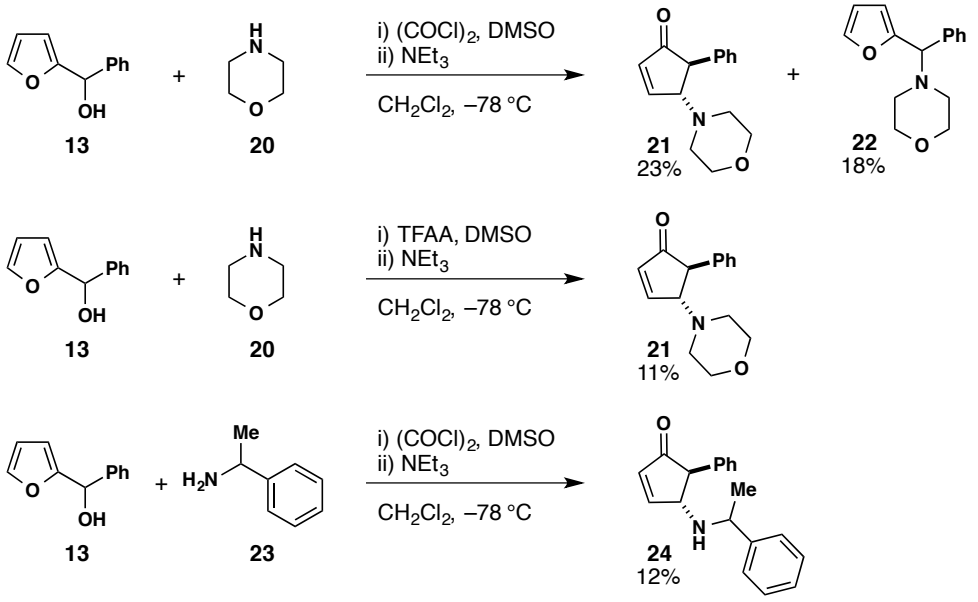
Scheme 9.3. Unexpected aza-Piancatelli rearrangement under Swern oxidation conditions.

Curious as to the generality of this surprising reaction, we set up the aza-Piancatelli rearrangement of phenyl furylcarbinol (**13**) and *p*-iodoaniline under Swern conditions, but found the reaction to be quite messy and only isolated the cyclopentenone **19** in 25% yield (Scheme 9.4).



Scheme 9.4. Swern-mediated aza-Piancatelli rearrangement.

Undeterred, we set up a reaction of phenyl furylcarbinol (**13**) with morpholine (**20**). To our delight, the desired cyclopentenone **21** formed in 23% yield, in addition to 18% of the substitution product **22** (Scheme 9.5). Switching to 1-phenylethan-1-amine (**23**), we were able to isolate 12% of the cyclopentenone **24** (Scheme 9.5). A few other experiments were completed, including the use of trifluoroacetic anhydride (TFAA) in the place of oxalyl chloride, changing the order of addition, and quenching with other bases, but thus far have not resulted in yields greater above 30%.



Scheme 9.5. Swern-mediated aza-Piancatelli rearrangements with non-aniline amines.

Although the Swern-mediated reaction does not perform as well as the dysprosium catalyzed rearrangement in the aniline case, it is much superior when using other amines. The reaction is especially intriguing from a mechanistic standpoint. We currently have two hypotheses as to the mode of activation. Our first hypothesis is that formation of **26** facilitates the formation of oxocarbenium **27**, which can be intercepted by the amine nucleophile and participate in the product-forming cascade (Figure 9.1). Alternatively, we have speculated that the chloride ion generated during the formation of the Swern reagent could displace the alcohol of the furylcarbinol, resulting in highly reactive alkyl chloride **29**, which can result in the formation of oxocarbenium **27** and rearrange upon attack of the amine nucleophile (Figure 9.1). Importantly, the amine nucleophile is not inhibited from reacting, unlike the dysprosium-catalyzed reaction, opening this transformation up to a whole host of other nucleophiles.

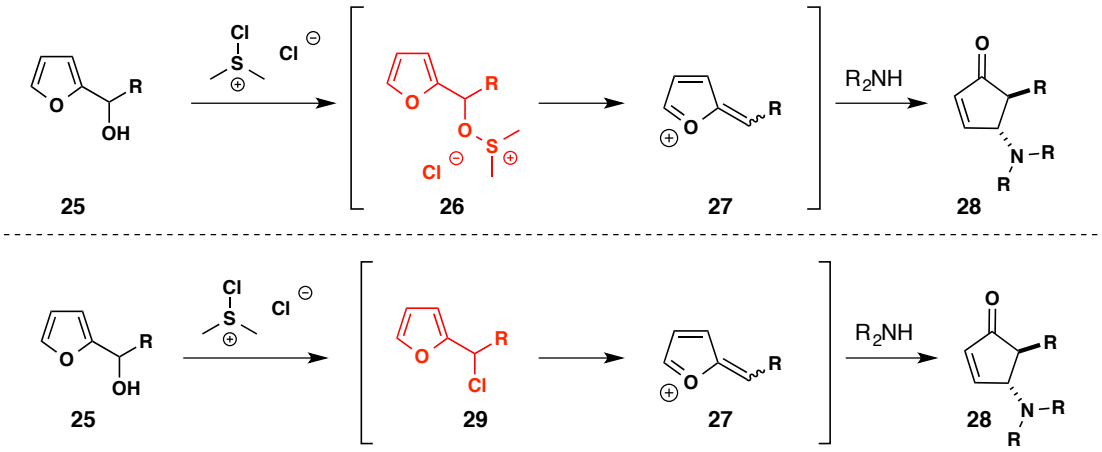


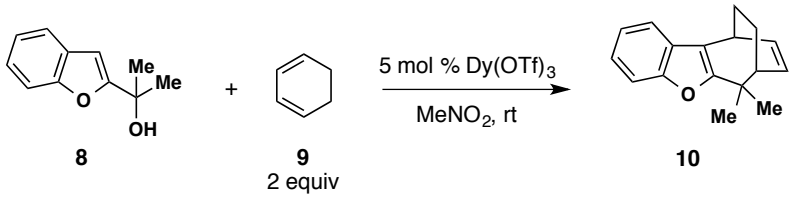
Figure 9.1. Proposed mechanisms for the Swern-mediated aza-Piancatelli rearrangement.

A thorough investigation of the Swern mediated aza-Piancatelli rearrangement could lead to a better understanding of the events that result in the product forming cascade, and could then be used to optimize reaction conditions for the aza-Piancatelli rearrangement with non-aniline amines – an exciting prospect.

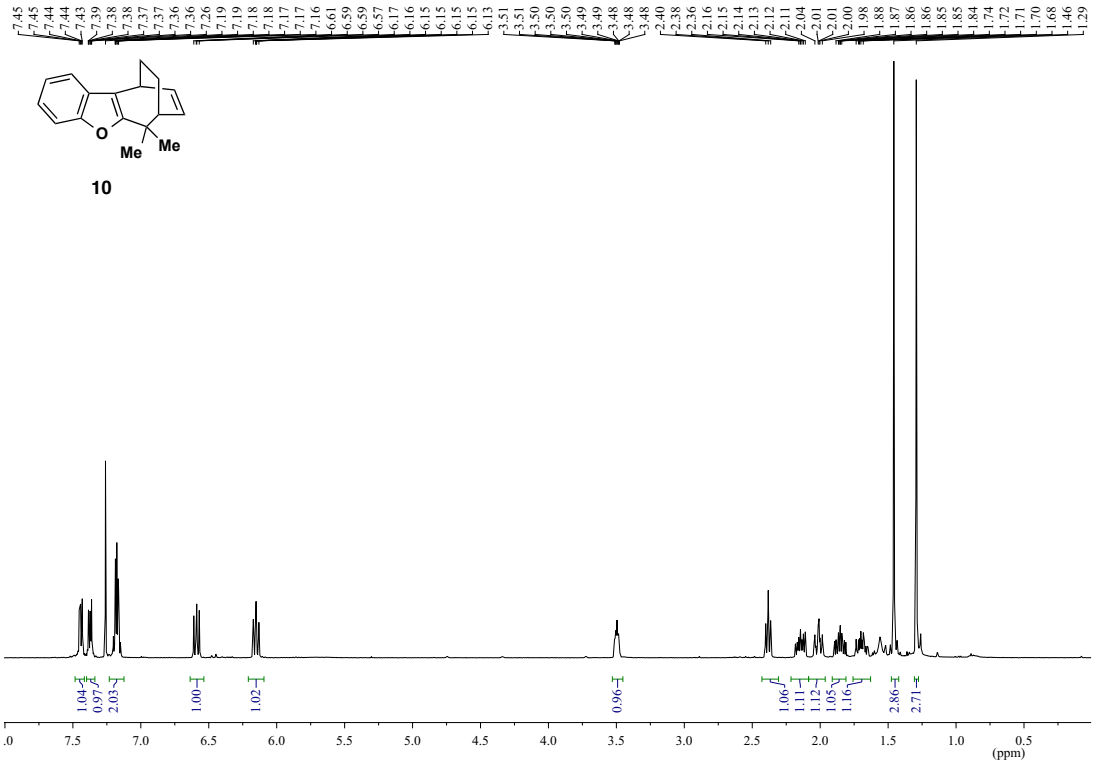
9.4. Experimental Procedures

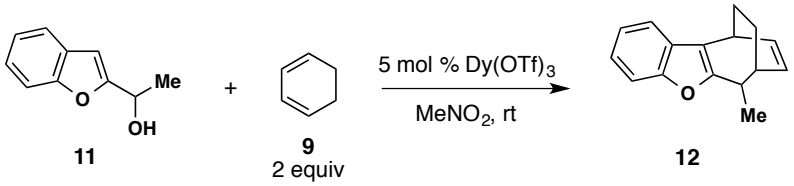
Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of air using reagent grade solvents. All commercially obtained reagents were used as received. Reaction temperatures were controlled using an Heidolph temperature modulator, and unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 ºC). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 pre-coated plates, (0.25 mm) and visualized by exposure to UV light (254 nm) or stained with anisaldehyde and potassium permanganate. Flash column chromatography was performed using normal phase silica gel (60 Å, 0.040 – 0.063 mm, Geduran). ^{1}H NMR spectra were recorded on Varian spectrometers (at 500 or 600 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and

integration. ^{13}C NMR spectra were recorded on Varian Spectrometers (125 or 150 MHz). Data for ^{13}C NMR spectra are reported in terms of chemical shift (δ ppm), multiplicity, coupling constant (Hz).



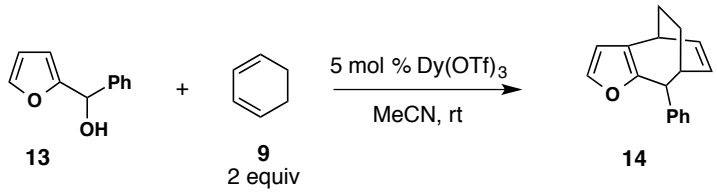
6,6-Dimethyl-7,10-dihydro-6*H*-7,10-ethanocyclohepta[*b*]benzofuran (10): A solution of furylcarbinol **8** (10.0 mg, 0.057 mmol) and cyclohexadiene **9** (11 μL, 0.11 mmol) in 0.6 mL $MeNO_2$ was treated with $Dy(OTf)_3$ (1.7 mg, 0.0028 mmol) and stirred at rt. After 18 h, no starting material was observable by TLC, and the reaction was quenched with saturated $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **10** (11.6 mg, 85%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.42 (m, 1H), 7.39 – 7.35 (m, 1H), 7.21 – 7.14 (m, 2H), 6.59 (dd, *J* = 8.8, 7.2 Hz, 1H), 6.15 (dd, *J* = 8.3, 7.8 Hz, 1H), 3.50 (ddd, *J* = 6.4, 4.1, 2.0 Hz, 1H), 2.38 (t, *J* = 7.2 Hz, 1H), 2.15 (ddd, *J* = 13.9, 9.6, 5.5 Hz, 1H), 2.01 (dddd, *J* = 9.6, 9.6, 2.6, 2.6 Hz, 1H), 1.85 (dddd, *J* = 11.9, 11.9, 5.5, 4.1 Hz, 1H), 1.69 (dddd, *J* = 14.0, 11.2, 7.1, 2.9 Hz, 1H), 1.46 (s, 3H), 1.29 (s, 3H) ppm.



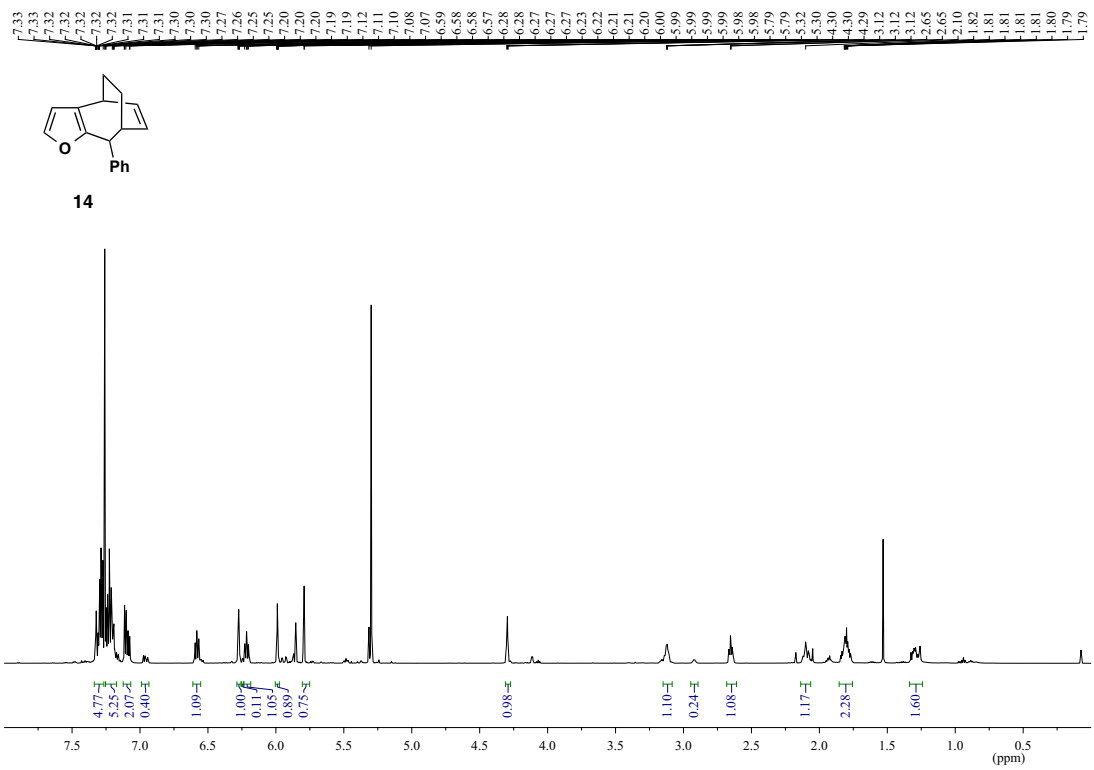


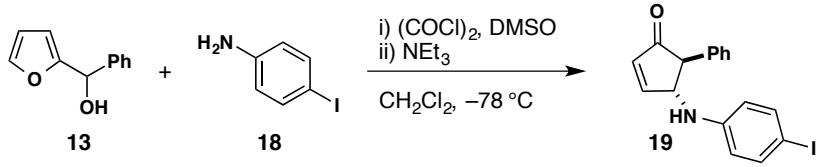
6-Methyl-7,10-dihydro-6*H*-7,10-ethanocyclohepta[*b*]benzofuran (12): A solution of furylcarbinol **11** (10.0 mg, 0.062 mmol) and cyclohexadiene **9** (12 µL, 0.11 mmol) in 0.6 mL $MeNO_2$ was treated with $Dy(OTf)_3$ (1.9 mg, 0.0030 mmol) and stirred at rt. After 18 h, no starting material was observable by TLC, and the reaction was quenched with saturated $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **12** (1.0 mg, 7%). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.41 (m, 1H), 7.40 – 7.34 (m, 1H), 7.22 – 7.13 (m, 2H), 6.70 – 6.64 (m, 0.3H), 6.58 (dd, *J* = 8.8, 7.2 Hz, 1H), 6.19 (ddd, *J* = 8.8, 7.4, 1.0 Hz, 1H), 6.06 – 5.99 (m,

0.3H), 3.50 (dddd, *J* = 6.0, 4.9, 2.2, 1.1 Hz, 1H), 3.17 (dddd, *J* = 9.9, 8.2, 6.6, 2.5 Hz, 1H), 3.09 (dddd, *J* = 7.1, 7.1, 7.1, 4.2 Hz, 0.3H), 2.76 (td, *J* = 7.3, 4.2 Hz, 0.3H), 2.51 (td, *J* = 7.3, 2.8 Hz, 1H), 2.12 – 2.00 (m, 2H), 2.00 – 1.74 (m, 2H), 1.70 – 1.59 (m, 1H), 1.45 (d, *J* = 7.1 Hz, 3H), 1.29 (d, *J* = 7.0 Hz, 0.9H) ppm.

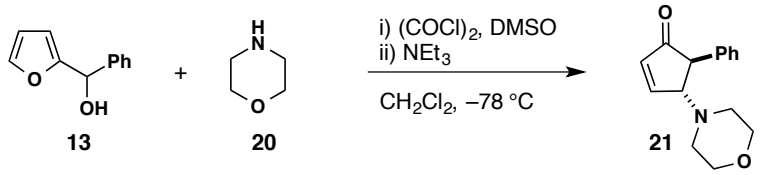


8-Phenyl-7,8-dihydro-4*H*-4,7-ethanocyclohepta[*b*]furan (14): A solution of furylcarbinol 13 (50.5 mg, 0.29 mmol) and cyclohexadiene **9** (55 µL, 0.58 mmol) in 1.5 mL MeCN was treated with $Dy(OTf)_3$ (9.1 mg, 0.015 mmol) and stirred at rt. After 24 h, no starting material was observable by TLC, and the reaction was quenched with saturated $NaHCO_3$ (5 mL), and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$, filtered and the solvent removed via rotary evaporation. The product was purified by flash column chromatography to give **14** (13 mg, 19%). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.34 – 7.17 (m, 4H), 7.14 – 7.05 (m, 1H), 6.58 (ddd, *J* = 9.0, 7.0, 2.2 Hz, 1H), 6.27 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.25 – 6.18 (m, 1H), 6.01 – 5.97 (m, 1H), 4.30 (dd, *J* = 3.2, 3.2 Hz, 1H), 3.15 – 3.09 (m, 1H), 2.65 (ddd, *J* = 7.2, 7.2, 3.2 Hz, 1H), 2.13 – 2.07 (m, 1H), 1.85 – 1.76 (m, 2H), 1.33 – 1.24 (m, 1H) ppm.

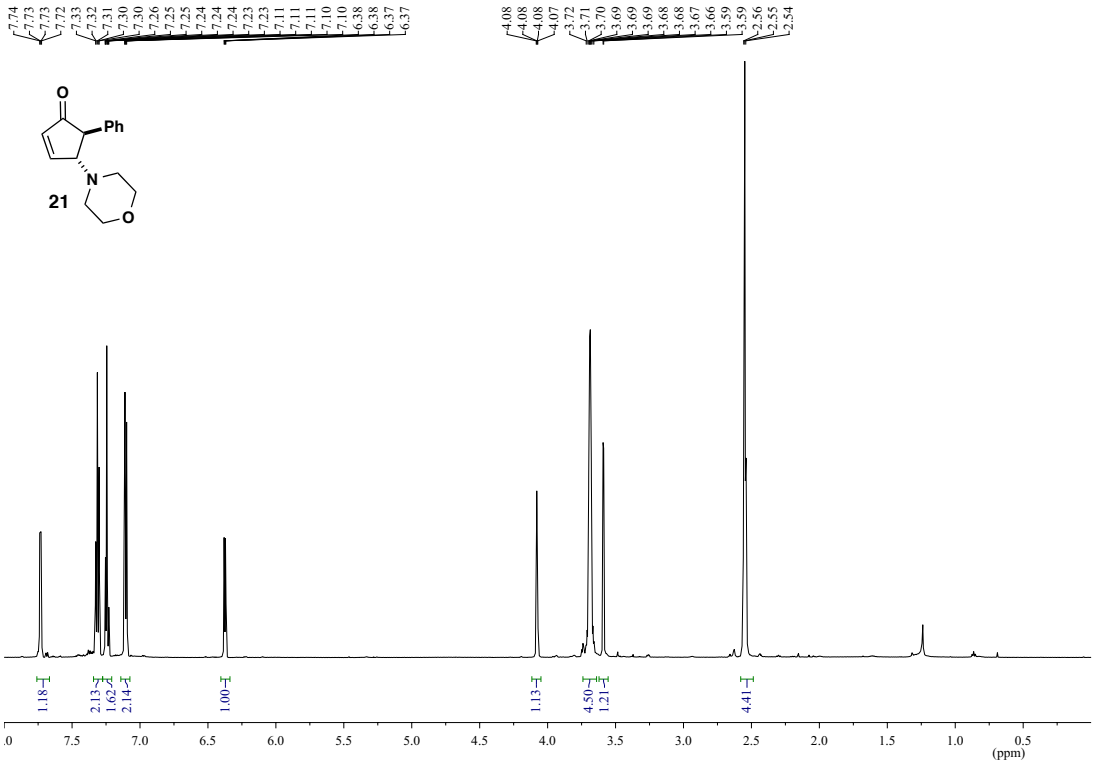


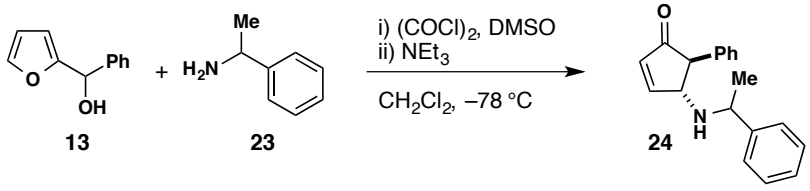


4-((4-Iodophenyl)amino)-5-phenylcyclopent-2-en-1-one (19): The Swern reagent was prepared by treating $(COCl)_2$ (58 µL, 0.69 mmol) in 3 mL dry CH_2Cl_2 at -78 °C with DMSO (65 µL, 0.92 mmol) via dropwise addition over 15 min. After 15 min, a solution of furylcarbinol **13** (100 mg, 0.57 mmol) and *p*-iodoaniline (125.7 mg, 0.57 mmol) in 1 mL dry CH_2Cl_2 was added via dropwise addition. The reaction was stirred at -78 °C for 45 min before it was quenched with NEt_3 (297 µL, 2.01 mmol) and allowed to come to rt. The resulting suspension was filtered through a pad of $MgSO_4$, washing with copious amounts of Et_2O. The solvent was removed via rotary evaporation and the product purified via flash column chromatography to give cyclopentenone **19** (52.2 mg, 25%) as a light brown oil.



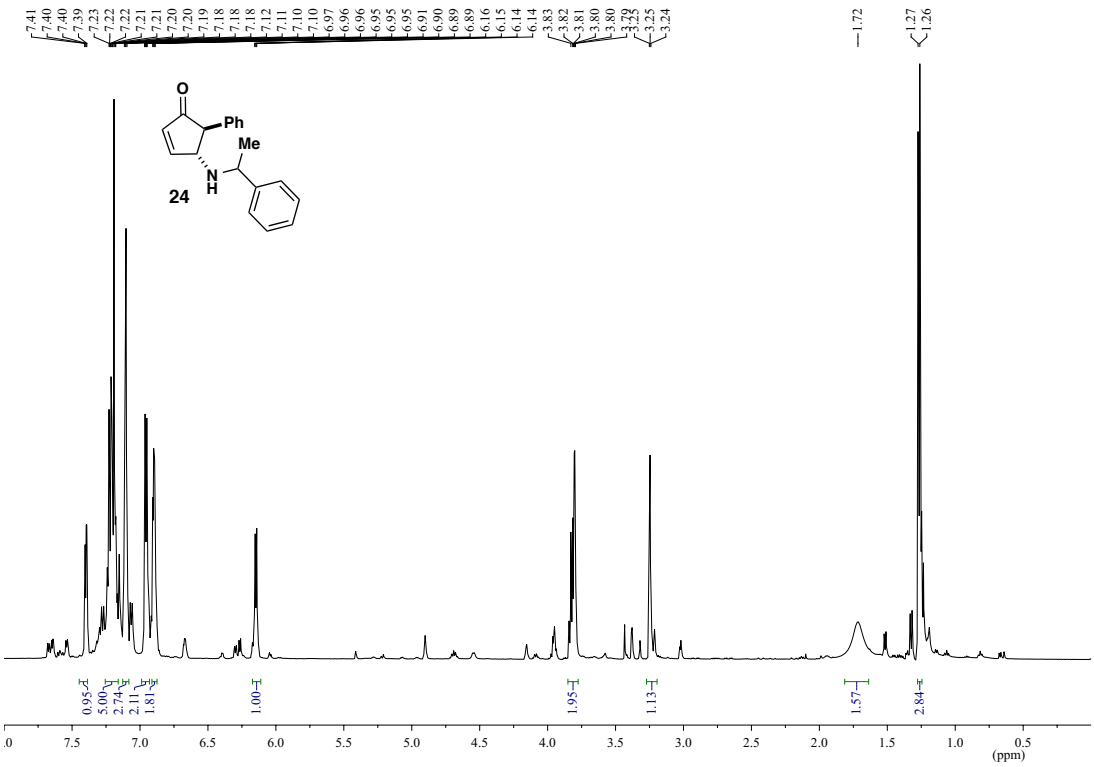
4-Morpholino-5-phenylcyclopent-2-en-1-one (21): The Swern reagent was prepared by treating $(COCl)_2$ (58 μL, 0.57 mmol) in 3 mL dry CH_2Cl_2 at -78 °C with DMSO (65 μL, 0.92 mmol) via dropwise addition over 15 min. After 15 min, a solution of furylcarbinol **13** (100 mg, 0.57 mmol) and morpholine (**20**) (50 μL, 0.57 mmol) in 1 mL dry CH_2Cl_2 was added via dropwise addition. The reaction was stirred at -78 °C for 45 min before it was quenched with NEt_3 (297 μL, 2.01 mmol) and allowed to come to rt. The resulting suspension was filtered through a pad of $MgSO_4$, washing with copious amounts of Et_2O. The solvent was removed via rotary evaporation and the product purified via flash column chromatography to give cyclopentenone **21** (31.9 mg, 23%) as a light brown oil. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.9, 2.3 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.21 (m, 1H), 7.11 (dd, *J* = 7.3, 1.5 Hz, 2H), 6.37 (dd, *J* = 5.9, 1.9 Hz, 1H), 4.08 (ddd, *J* = 2.3, 2.3, 2.3 Hz, 1H), 3.69 (ddd, *J* = 4.2, 4.2, 2.0 Hz, 4H), 3.59 (d, *J* = 2.7 Hz, 1H), 2.55 (dd, *J* = 4.6, 4.6 Hz, 4H) ppm.





5-Phenyl-4-((1-phenylethyl)amino)cyclopent-2-en-1-one (24): The Swern reagent was prepared by treating $(COCl)_2$ (58 µL, 0.57 mmol) in 3 mL dry CH_2Cl_2 at -78 °C with DMSO (65 µL, 0.92 mmol) via dropwise addition over 15 min. After 15 min, a solution of furylcarbinol **13** (100 mg, 0.57 mmol) and 1-phenylethan-1-amine (**23**) (50 µL, 0.57 mmol) in 1 mL dry CH_2Cl_2 was added via dropwise addition. The reaction was stirred at -78 °C for 45 min before it was quenched with NEt_3 (297 µL, 2.01 mmol) and allowed to come to rt. The resulting suspension was filtered through a pad of $MgSO_4$, washing with copious amounts of Et_2O. The solvent was removed via rotary evaporation and the product purified via flash column chromatography to give cyclopentenone **24** (31.9 mg, 23%) as a light

brown oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 5.9, 2.4 Hz, 1H), 7.24 – 7.17 (m, 4H), 7.12 – 7.09 (m, 2H), 6.97 – 6.93 (m, 2H), 6.90 (dd, *J* = 6.7, 3.0 Hz, 2H), 6.15 (dd, *J* = 5.7, 1.9 Hz, 1H), 3.85 – 3.78 (m, 2H), 3.25 (d, *J* = 2.7 Hz, 1H), 1.72 (bs, 1H), 1.27 (d, *J* = 6.5 Hz, 3H) ppm.



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